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(71) Applicants (for all designated States except US):
DANA-FARBER CANCER INSTITUTE, INC. [US/US]; 44 Binney Street, Boston, MA 02115 (US).
TRUSTEES OF BOSTON UNIVERSITY [US/US]; 147 Bay State Road, Boston, MA 02215 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SCHULTZE,**

Joachim, L. [DE/US]; 37 Auburn Street, Brookline, MA 02146 (US). **VONDERHEIDE, Robert, H.** [DE/US]; Apartment 801, 1284 Beacon Street, Brookline, MA 02115 (US). **SHERR, David** [US/US]; 39 Hastings Street, West Roxbury, MA 02132 (US). **NADLER, Lee, M.** [US/US]; 36 Cross Hill Road, Newton, MA 02159 (US). **MAECKER, Britta** [DE/US]; 368 Longwood Avenue, #21, Boston, MA 02215 (US). **VON BERGWELT-BAILDON, Michael** [DE/US]; 24 A Prentiss Street, Cambridge, MA 02140 (US).

(74) Agent: **CLARK, Paul, T.**; Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110-2214 (US).

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(54) Title: CANCER IMMUNOTHERAPY AND DIAGNOSIS USING CYTOCHROME P450 1B1

(57) Abstract: The invention provides methods for conducting cancer immunotherapy and diagnosis using cytochrome P450 1B1 and peptide fragments thereof.

CANCER IMMUNOTHERAPY AND DIAGNOSIS USING
CYTOCHROME P450 1B1

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Background of the Invention

This invention relates to the prevention, treatment, and diagnosis of cancer.

10 The paucity of clinically significant anti-tumor immune responses in cancer patients has long suggested that antigen-specific immunotherapy would not play a significant role in cancer treatment. However, pioneering studies in the early 1990s, using tumor-specific cytotoxic T lymphocytes (CTLs) from cancer patients, showed the existence of human tumor associated antigens (TAAs). This 15 led to the suggestion that such antigens could be used to stimulate therapeutic anti-tumor immune responses in patients. Although these studies focused primarily on melanoma, TAAs have also been characterized in several other malignancies (Van Pel *et al.*, *Immunological Reviews* 145:229-250, 1995; Rosenberg, *Immunol. Today* 18:175-182, 1997; Van den Eynde *et al.*, *Curr. Opin. Immunol.* 9:684-693, 1997), raising the hypothesis that most, if not all, tumors 20 express antigens that can be used to induce CTL-mediated tumor destruction. Consequently, clinical efforts are now underway to target TAAs in strategies, such as vaccination and adoptive T cell therapy, to generate effective anti-tumor CTL responses in patients.

25 The demonstration that TAA-specific immune responses can lead to tumor regression has been borne out extensively in animal models (Rosenberg, *Immunity* 10:281-287, 1999). Although the identification of TAAs using patients' CTLs has revitalized the field of T cell immunotherapy, these methods are slow, very expensive, and labor-intensive. Moreover, the strategy relies on 30 the generation of tumor-specific T cell clones *in vitro*, suggesting that only a restricted set of TAAs will be identified by this method. With these limitations in mind, Pfreundschuh and colleagues developed an alternative approach, SEREX

(serological identification of antigens by recombinant expression cloning), to identify TAAs (Sahin *et al.*, *Curr. Opin. Immunol.* 9:709-716, 1997). SEREX makes use of patients' antibody responses to tumor-derived genes and this strategy has accelerated the identification of TAAs significantly. Although 5 several T cell-defined TAAs, such as the MAGE genes, have also been identified by SEREX, there is no information available about CTL epitopes for the vast majority of genes in the SEREX database, and, of course, such epitopes are required to activate a CTL response.

Although there is no doubt that the identification of numerous TAAs by 10 CTL-based approaches or SEREX reflects the existence of an anti-tumor immune response, it remains to be determined if these antigens play a role as tumor regression antigens (Sarma *et al.*, *J. Exp. Med.* 189:811-820, 1999). Indeed, most 15 T cell epitopes in TAAs identified by patient CTLs have been demonstrated to be of low MHC binding affinity and/or low MHC/peptide complex stability. This quality distinguishes TAA-derived peptides from viral peptides that are almost exclusively of high binding affinity and high MHC/peptide complex stability (Feltkamp *et al.*, *Mol. Immunol.* 31:1391-1401, 1994; Sette *et al.*, *J. Immunol.* 153:5586-5592, 1994). Clinical vaccination trials have circumvented this 20 obstacle by utilizing altered peptides with higher MHC binding affinity and higher MHC/peptide complex stability (Rosenberg *et al.*, *Nat. Med.* 4:321-327, 1998). The low binding affinity of TAA-derived peptides is likely to be one of the reasons why natural CTL responses against such peptides are not successful 25 for tumor eradication. This is in agreement with the finding that large numbers of TAA-specific CTLs co-exist with metastatic tumors in melanoma patients (Romero *et al.*, *J. Exp. Med.* 188:1641-1650, 1998). A recent study has even demonstrated that despite expansion, such CTLs were hyporesponsive, showing reduced cytotoxic and cytokine responses (Lee *et al.*, *Nat. Med.* 5:677-685, 1999).

In addition, most TAAs described thus far are expressed in only one or a few tumor types, and not all patients with a given tumor type express the 30 associated TAA. As a result, progress in the field of cancer immunotherapy has been relatively slow, because it has not been possible to develop widely useful

TAA-specific immunotherapeutic strategies. Not only has it been necessary to tailor such therapies to individual types of malignancies, in some cases (such as the immunoglobulin idiotypic antigen in B cell malignancies), it has been necessary to tailor these therapies to individual patients.

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Summary of the Invention

The invention provides a method of treating a patient that has or is at risk of having a cell that expresses cytochrome P450 1B1 (CYP1B1). This method involves administering to the patient a cytotoxic T lymphocyte (CTL)(autologous or allogeneic) that leads to death of (from here on said as kill) the cell in a CYP1B1-specific, major histocompatibility complex-restricted fashion. The CTL can be generated, for example, by activation with an antigen presenting cell that has been pulsed with CYP1B1, or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule.

15 The invention also includes a second method of treating a patient that has or is at risk of having a cell that expresses CYP1B1. This method involves administering to the patient an antigen presenting cell (APC) that activates in the patient a cytotoxic T lymphocyte that kills the cell in a CYP1B1-specific, major histocompatibility complex-restricted fashion. The APC can be pulsed with 20 CYP1B1 or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule.

25 Another method included in the invention is a third method of treating a patient that has or is at risk of having a cell that expresses CYP1B1. This method involves administering to the patient CYP1B1 or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule, which is processed by an antigen presenting cell in the patient, which, in turn, activates a cytotoxic T lymphocyte in the patient to induce cell death of the cell that expresses CYP1B1 in a CYP1B1-specific, major histocompatibility complex-restricted fashion. The CYP1B1 polypeptide or peptide of CYP1B1 used in this method can be administered to the 30 patient in association with an adjuvant.

The invention also includes a fourth method of treating a patient that has or is at risk of having a cell that expresses CYP1B1. This method involves administering to the patient a nucleic acid molecule encoding CYP1B1 or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule.

5 The nucleic acid molecule is expressed in the patient so that it can be processed by an antigen presenting cell in the patient, which activates a cytotoxic T lymphocyte in the patient to induce cell death of the cell that expresses CYP1B1, in a CYP1B1-specific, major histocompatibility complex-restricted fashion. The nucleic acid molecule encoding CYP1B1 or a peptide of CYP1B1 can be present in an expression vector.

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Each of the methods described above can also include treatment based around a second (or more) tumor associated antigen, *e.g.*, telomerase (hTERT, PCT/US99/25438), or a peptide thereof that binds to MHC (*e.g.*, the I540 peptide).

15 In any of the methods described above, the patient can have a tumor containing cells that express CYP1B1. APCs used in these methods can be, for example, a dendritic cell or a CD40-activated B cell. The peptide of CYP1B1 in these methods can bind to a class I or a class II major histocompatibility complex (MHC) molecule. In the case of a class I MHC molecule, the molecule can be, 20 for example, an HLA-A2 molecule, and the peptide of CYP1B1 can include the amino acid sequence of CYP239 (SEQ ID NO:1; SLVDVMPWL), CYP246 (SEQ ID NO:2; WLQYFPNPI), CYP190 (SEQ ID NO:3; FLDPRPLTV), or CYP528 (SEQ ID NO:4; LLDSAVQNL). Examples of other CYP1B1 sequences that can be used in these methods are set forth in the Sequence Appendix and in Tables 3- 25 10.

The invention also includes a method of assessing the level of immunity of a patient to CYP1B1 or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule. In this method, the level of cytotoxic T lymphocytes specific for CYP1B1 or a peptide of CYP1B1 is measured in a 30 sample from a patient. The sample can be obtained from the patient before,

during, or after a cancer treatment is administered to the patient. A sample can also be obtained, for example, before and after treatment.

The invention also includes CYP1B1 peptides that bind to major histocompatibility complex molecules, for example, a peptide that consists 5 essentially of the amino acid sequence set forth in SEQ ID NO:1 (CYP239), SEQ ID NO:2 (CYP246), SEQ ID NO:3 (CYP190), or SEQ ID NO:4 (CYP528).

Also included in the invention is an *ex vivo* generated cytotoxic T lymphocyte that specifically kills a cell expressing CYP1B1 in a specific, major histocompatibility complex-restricted fashion, and an *ex vivo* generated antigen presenting cell (e.g., a dendritic cell or a CD40-activated B cell) that presents a peptide of CYP1B1 in the context of a major histocompatibility complex molecule. 10

As is understood in the art, a “polypeptide” is a chain of amino acids linked to one another by peptide bonds. A “protein” can be made up of one or 15 more polypeptides, while a “peptide” is generally understood to be (or include) a fragment of a polypeptide, and to consist of a chain of peptide bond-linked amino acids that is shorter in length than a full length polypeptide from which it may be derived.

A “tumor associated antigen,” such as CYP1B1, is an immunogenic 20 molecule, such as a protein, that is, generally, expressed at a higher level in tumor cells than in non-tumor cells, in which, preferably, it may not be expressed at all, or only at low levels. A tumor associated antigen, or TAA, is said to be “universal” if it is expressed in tumors of different origins.

A “cytochrome P450 1B1 polypeptide,” or a “CYP1B1 polypeptide” is 25 a full length, non-fragmented polypeptide of CYP1B1, while a “cytochrome P450 1B1 peptide,” or a “CYP1B1 peptide,” is (or includes) a fragment of such a CYP1B1 polypeptide. CYP1B1 peptides can be of any length, up to just under the full length of a CYP1B1 polypeptide. However, preferably, for use in the invention, CYP1B1 peptides are of a relatively short length, such as, for example, 30 eight, nine, ten, eleven, or twelve amino acids. Also, a CYP1B1 peptide may include sequences that are not present in a corresponding CYP1B1 polypeptide,

provided that the CYP1B1 peptide also includes a stretch of at least, for example, eight, nine, ten, eleven, or twelve consecutive amino acids that have a sequence that is identical to a sequence of eight, nine, ten, eleven, or twelve consecutive amino acids in a CYP1B1 polypeptide.

5 Peptides including amino acid substitutions can also be considered as CYP1B1 peptides. For example, a CYP1B1 peptide can include a region of at least nine amino acids, of which any six or more are identical to the amino acids within a nine amino acid stretch in CYP1B1. Preferably, at least seven, more preferably, at least eight, and, most preferably, all nine of the amino acids in a
10 CYP1B1 peptide nine amino acid region are identical to a nine amino acid region in the CYP1B1.

A CYP1B1 polypeptide corresponding to CYP1B1 includes 533 amino acids that are substantially identical (see below) to the amino acid sequence of CYP1B1 (Sutter *et al.*, J. Biol. Chem. 269:13092-13099, 1994; Tang *et al.*, J. Biol. Chem. 271:28324-28330, 1996; Genbank Accession No. U56438), or such a polypeptide can include the amino acid sequence of CYP1B1, as well as additional sequences.

As is discussed further below, it is preferable that CYP1B1 polypeptides of the invention include regions that bind to major histocompatibility complex (MHC) antigens. Preferred examples of CYP1B1 peptides that are included in the invention are CYP239 (SEQ ID NO:1), CYP246 (SEQ ID NO:2), CYP190 (SEQ ID NO:3), and CYP528 (SEQ ID NO:4). Additional CYP1B1 peptides are listed in the Sequence Appendix, as well in Tables 3-10, and still more CYP1B1 peptides can be identified using methods described below (also see
25 PCT/US99/25438).

A CYP1B1 peptide or polypeptide can be fused to amino acid sequences that do not naturally occur in CYP1B1. Moreover, a CYP1B1 peptide or polypeptide can be attached to the surface of a cell or to a molecule or a macromolecule (*e.g.*, a histocompatibility antigen), or a CYP1B1 peptide or
30 polypeptide can be conjugated to immunogens or adjuvants that are known to those of skill in this art, for example, keyhole limpet hemocyanin (KLH), for the

purpose of eliciting a CYP1B1-specific immune response. As is noted above, preferred examples of CYP1B1 peptides are CYP239 (SEQ ID NO:1), CYP246 (SEQ ID NO:2), CYP190 (SEQ ID NO:3), and CYP528 (SEQ ID NO:4).

5 By "CYP1B1 nucleic acid molecule" is meant a DNA or RNA (*e.g.*, mRNA) molecule that encodes a CYP1B1 polypeptide or CYP1B1 peptide, as are defined above.

By "CYP1B1-expressing tumor cell" is meant a tumor cell that expresses CYP1B1. A CYP1B1-expressing tumor cell can express a level of CYP1B1 that is equal to, or, preferably, greater than the level of CYP1B1 expressed by the normal cell type from which the CYP1B1-expressing tumor cell has originated, or other non-tumor cells. Preferably, the tumor cell expresses at least 10% more CYP1B1, more preferably, at least 25% more, still more preferably at least 50% more, and most preferably at least 150% more CYP1B1 than the normal cell type from which the CYP1B1-expressing tumor cell has originated, or another non-tumor cell. CYP1B1 expression levels in a CYP1B1-expressing tumor cell can be increased by, for example, increased transcription of the CYP1B1 gene, increased CYP1B1 mRNA stability or translation, increased CYP1B1 polypeptide stability, or increased CYP1B1 enzymatic activity. Increasing such CYP1B1 expression levels may be useful in the invention to 20 increase the likelihood that a tumor cell will be recognized as a target of the immunotherapeutic methods described herein (see below).

By "histocompatibility antigen" is meant a molecule, such as a major histocompatibility complex (MHC) class I, MHC class II, or minor histocompatibility antigen, that mediates interactions of cells of the immune system with each other and with other cell types. Examples of histocompatibility antigens include MHC class I antigens, such as HLA-A (*e.g.*, A1, A2, A3, A11, A24, A31, A33, and A38), HLA-B, and HLA-C, MHC class II antigens, such as HLA-DR, HLA-DQ, HLA-DX, HLA-DO, HLA-DZ, and HLA-DP, and minor histocompatibility antigens, such as HA-1.

By "generating CTLs" is meant an *in vivo*, *in vitro*, or *ex vivo* process by which CTLs (*e.g.*, CYP1B1-specific CTLs) are activated (*e.g.*, stimulated to grow and divide) and/or selected.

A peptide of CYP1B1 is said to "specifically bind" to an MHC antigen 5 if the peptide adheres to a histocompatibility antigen under physiological conditions. For example, such binding can be similar to that of a peptide antigen that is naturally processed and presented in the context of MHC in an antigen presenting cell.

A cytotoxic T lymphocyte (CTL) or antibody is said to "specifically 10 recognize" a CYP1B1 polypeptide or a CYP1B1 peptide if it binds to the polypeptide or peptide, but does not substantially bind to other, unrelated polypeptides or peptides.

A CTL is said to "specifically kill" a cell if it specifically recognizes 15 and lyses a cell that expresses an antigen (*e.g.*, CYP1B1) to which it has been activated, but does not substantially recognize or lyse cells not expressing the antigen. In the case of CYP1B1, such a CTL is designated as a "CYP1B1-specific CTL" herein.

By "CYP1B1-specific antibody" is meant an antibody that can 20 specifically recognize and bind to a CYP1B1 peptide or polypeptide, and that does not substantially recognize and bind to other, unrelated molecules.

A CYP1B1 polypeptide is "presented" if a peptide of CYP1B1 is displayed on the extracellular surface of a cell (*e.g.*, an antigen presenting cell), such that it can result in the *in vivo*, *ex vivo*, or *in vitro* generation of CYP1B1-specific CTLs or the lysis of a tumor cell by a CYP1B1-specific CTL. Preferably, 25 the displayed CYP1B1 peptide is bound to a histocompatibility antigen.

By "physiological conditions" is meant the *in vivo* environment in which CYP1B1-specific CTLs are generated (activated and/or selected) and perform their biological functions (*e.g.*, recognition of a CYP1B1 peptide and MHC-restricted lysis of CYP1B1-expressing tumor cells), or an *in vitro* or *ex vivo* 30 environment that allows CYP1B1-specific CTLs to be generated and to perform their biological functions.

By "CYP1B1 vaccination" is meant administration of an immunogenic preparation including one or more CYP1B1 peptides, CYP1B1 polypeptides, CYP1B1 nucleic acid molecules, fragments of any of these molecules, CYP1B1-presenting cells (e.g., dendritic cells or CD40-activated B cells), or mixtures thereof. Vaccination is performed on a subject who has a tumor, has a history of having a tumor or tumors, is likely to develop a tumor, or any healthy individual to prevent tumors, or on a subject in which CYP1B1-specific immune cells (such as CTLs) are to be generated for transfer into a patient. Such vaccination stimulates a CYP1B1-specific immune response within the subject. In subjects having tumors, the vaccination can result in partial or complete inhibition of tumor growth, or partial or complete tumor regression, provided that the patient's tumor expresses CYP1B1. In addition, vaccination can provide prophylaxis against the development of new CYP1B1-expressing tumors.

A "vaccine," as used herein, is an immunogenic composition that can be administered in the vaccination method described above. Thus, a vaccine includes, for example, one or more CYP1B1 peptides, CYP1B1 polypeptides, CYP1B1 nucleic acid molecules, fragments of any of these molecules, CYP1B1-presenting cells (e.g., dendritic cells or CD40-activated B cells), or mixtures thereof. Optionally, a vaccine composition can also include an adjuvant, which is a molecule that stimulates an immune response to a co-administered vaccine antigen. Examples of adjuvants that can be used in the invention are provided below. A vaccine composition can also include other tumor associated antigens (e.g., hTERT) or peptides thereof (PCT/US99/25438).

By "immune cell" is meant any cell that plays a role in cell-mediated or humoral immunity, including CTLs and antigen-presenting cells, e.g., B cells, T helper cells, and dendritic cells.

By "sample" is meant a tumor or tissue biopsy, a lymph node biopsy, bone marrow, cells, blood, serum, urine, stool, sputum, saliva, or other specimen obtained from a patient. A sample can be analyzed to determine the level of CYP1B1-specific CTLs, the level of CYP1B1-specific antibodies, or the level of any other immune response indicator (e.g., a cytokine) in the patient from whom

it was taken by methods that are known in the art. For example, ELISA can be used to measure levels of CYP1B1-specific antibodies, and ELISPOT can be used to measure cytokine levels. Also, Cr⁵¹ release (T cell cytotoxicity) assays and assays that test the binding of CTLs to tetrameric CYP1B1 peptide/MHC complexes, as described herein, can be used to measure levels of CYP1B1-specific CTLs.

By "reference sample" is meant a sample in which the level of CYP1B1-specific CTLs or the level of CYP1B1-specific antibodies have been measured, and to which the level of CYP1B1-specific CTLs or the level of CYP1B1-specific antibodies in a test subject's sample are compared. Reference levels can be higher, lower, or the same as patient sample levels. Comparison of a test sample to a reference sample provides an assessment of the CYP1B1-specific immune response in the test subject. In addition, comparison of a patient's sample levels to reference sample levels can allow a diagnosis of cancer and/or a prognosis of a cancer in a patient having a tumor that includes CYP1B1-expressing cells.

By "cancer treatment" is meant any therapy (e.g., chemotherapy, radiation therapy, administration of a tumor associated antigen (e.g., CYP1B1)-specific CTLs, administration of an APC presenting a peptide of a TAA (e.g., CYP1B1), or vaccination with a TAA (e.g., CYP1B1), a nucleic acid molecule encoding a TAA (e.g., CYP1B1), or a fragment thereof, to enhance an anti-tumor immune response) administered either alone or in combination with other therapies, that alleviates disease in at least some patients to which the treatment is administered. For example, a cancer treatment can reduce or inhibit tumor growth, or can induce partial or complete tumor regression. Furthermore, a cancer treatment can be prophylactic, in that it inhibits or prevents the development of new tumors in healthy individuals, in patients that are in remission from cancer, have metastatic cancer, or have a high risk of developing cancer.

By "inhibiting the development of a tumor" is meant administering a protective therapy (such as CYP1B1-specific CTLs, CYP1B1 peptide presenting APCs, or a vaccine including, for example, one or more CYP1B1 peptides, CYP1B1 polypeptides, or CYP1B1 nucleic acid molecules, or a combination thereof) to a subject adjudged to have a higher than average risk of developing a tumor. Subjects with a relatively high risk of developing a tumor include those having a family history of cancer, those having one or more genetic mutations that are associated with a high risk for cancer (e.g., a mutation that inactivates a tumor suppressor gene), those having relatively high levels of CYP1B1-specific CTLs or 5 CYP1B1-specific antibodies, those who have cancer or are in remission from cancer, and those who have been exposed to agents known or suspected to cause 10 cancer.

By "pharmaceutically acceptable carrier" is meant a carrier that is physiologically acceptable to a treated patient, while retaining the therapeutic 15 properties of the compound with which it is administered. One exemplary pharmaceutically acceptable carrier is physiological saline. Other physiologically acceptable carriers and their formulations are known to those skilled in the art, and are described, for example, in *Remington's Pharmaceutical Sciences* (18th edition), ed. A. Gennaro, 1990, Mack Publishing Company, Easton, PA.

20 The term "substantially identical" is used herein to describe a polypeptide or nucleic acid molecule exhibiting at least 50%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% identity to a reference amino acid or nucleic acid sequence. For polypeptides, the length of comparison sequences is at least 8 amino acids, preferably at least 16 amino acids, 25 more preferably at least 25 amino acids, and most preferably 35 amino acids. For nucleic acid molecules, the length of comparison sequences is at least 24 nucleotides, preferably at least 50 nucleotides, more preferably at least 75 nucleotides, and most preferably at least 110 nucleotides. Sequence identity is typically measured using sequence analysis software with the default parameters 30 specified therein (e.g., Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710

University Avenue, Madison, WI 53705). The CYP1B1 polypeptides, peptides, and nucleic acid molecules of the invention can be identical or substantially identical to naturally occurring molecules, and thus may or may not include non-wild type sequences.

5 By "substantially pure peptide" or "substantially pure polypeptide" is meant a peptide, polypeptide, or a fragment thereof, which has been separated from the components that naturally accompany it. Typically, the peptide or polypeptide is substantially pure when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally 10 associated. Preferably, the peptide or polypeptide is a CYP1B1 peptide or polypeptide that is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, pure. A substantially pure CYP1B1 peptide or polypeptide can be obtained, for example, by extraction from a natural source (e.g., a tumor cell), by expression of a recombinant nucleic acid molecule 15 encoding a CYP1B1 peptide or polypeptide, or by chemically synthesizing the peptide or polypeptide. Purity can be measured by any appropriate method, e.g., by column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

A protein is substantially free of naturally associated components when 20 it is separated from those contaminants that accompany it in its natural state. Thus, a protein that is chemically synthesized or produced in a cellular system different from the cell from which it naturally originates is substantially free from its naturally associated components. Accordingly, substantially pure peptides and polypeptides not only include those derived from eukaryotic organisms, but also 25 those synthesized in *E. coli* or other prokaryotes.

By "substantially pure DNA" or "isolated DNA" is meant DNA that is free of the genes that, in the naturally-occurring genome of the organism from which the DNA is derived, flank the gene. The term thus includes, for example, a recombinant DNA that is incorporated into a vector; an autonomously replicating 30 plasmid or virus; or the genomic DNA of a prokaryote or eukaryote; or DNA that exists as a separate molecule (e.g., a cDNA, or a genomic or cDNA fragment

produced by PCR or restriction endonuclease digestion) independent of other sequences. It also includes a recombinant DNA that is part of a hybrid gene encoding additional polypeptide sequence.

By "transformation," "transfection," or "transduction" is meant any 5 method for introducing foreign molecules into a cell. Lipofection, DEAE-dextran-mediated transfection, microinjection, protoplast fusion, calcium phosphate precipitation, transduction (*e.g.*, bacteriophage, adenoviral retroviral, or other viral delivery), electroporation, and biolistic transformation are just a few of the methods known to those skilled in the art that can be used in the invention.

10 By "transformed cell," "transfected cell," or "transduced cell," is meant a cell (or a descendent of a cell) into which a nucleic acid molecule (*e.g.*, a DNA or RNA molecule) encoding a polypeptide of the invention has been introduced by means of recombinant DNA techniques.

15 By "promoter" is meant a minimal sequence sufficient to direct transcription. Promoter elements that are sufficient to render promoter-dependent gene expression controllable for cell type-specific, tissue-specific, temporal-specific, or inducible by external signals or agents can also be used in the invention; such elements can be located in the 5' or 3' or intron sequence regions of the native gene.

20 By "operably linked" is meant that a gene and one or more regulatory sequences are connected in such a way as to permit gene expression when the appropriate molecules (*e.g.*, transcriptional activator proteins) are bound to the regulatory sequences.

25 By "expression vector" is meant a genetically engineered plasmid or virus, derived from, for example, a bacteriophage, adenovirus, retrovirus, poxvirus, herpesvirus, or artificial chromosome, that is used to transfer a peptide or polypeptide coding sequence (*e.g.*, a CYP1B1 peptide coding sequence), operably linked to a promoter, into a host cell, such that the encoded peptide or polypeptide is expressed within the host cell.

Other features and advantages of the invention will be apparent from the drawings, following detailed description, and the claims.

Brief Description of the Drawings

5 Fig. 1 is a graph showing the level of peptide binding of MAGE-3, CYP239, and CYP246 to TAP-deficient T2 cells.

Figs. 2A-2D are graphs showing that CTL derived from healthy donors recognize CYP239 and CYP246 peptides. (A) CTL raised against the CYP239 peptide specifically lyse CYP239 pulsed (■), but not unpulsed T2 cells (□), or T2 cells 10 pulsed with an irrelevant peptide (○; F271 from MAGE-3). (B) Similarly, CTL generated against the CYP246 peptide recognize only T2 cells pulsed with CYP246 (■), but not control T2 cells (□, unpulsed; ○, pulsed with F271). The diagrams display representative experiments for 11/13 healthy donors positive for CYP239-specific CTL induction and 4/10 healthy donors positive for CYP246-specific CTL induction. (C) CYP239-specific CTL recognize autologous CD40-B 15 cells pulsed with CYP239 peptide (◆), but not unpulsed autologous CD40-B (◇) or allogeneic HLA-A2 mismatched CD40-B unpulsed (○) or pulsed with CYP239 peptide (●). (D) Analogous results were obtained for CYP246-specific CTL using the same target cells unpulsed or pulsed with the CYP246 peptide.

20 Fig. 2E is a series of graphs showing a representative tetramer analysis of CYP239- and CYP246-specific CTL after 4 weeks in culture. The A2/TAX tetramer served as a negative control. Percent tetramer⁺ CD8⁺ T cells is shown. Positive tetramer staining correlated with specific cytotoxicity in ⁵¹Cr assays.

25 Fig. 2F is a graph showing the cytotoxicity of expanded CYP239-specific tetramer sorted CTL against T2 cells either unpulsed (□), pulsed with CYP239 (■) or RT-pol476 (○).

Fig. 3 is a graph showing the level of specific lysis of CD40-activated B cells that were titrated with increasing concentrations of peptide before exposure to peptide-specific CTLs.

Figs. 4A-4H are graphs showing that CYP239 and CYP246-specific CTL are cytotoxic for HLA-A2⁺ melanoma, multiple myeloma and ovarian carcinoma cell lines. Expression of CYP1B1 in all tumor cell lines was confirmed by Western blot analysis. HLA-A2⁺ cell lines are shown by solid symbols; HLA-A2⁻ cell lines by open symbols. Targets for CYP239-specific CTL (upper panel) and CYP246-specific CTL (lower panel) were (A, B) melanoma cell lines K029 (●) and SK-MEL-2 (○), (C, D) multiple myeloma cell lines U266 (●), IM-9 (◆) and HS-Sultan (◇), and (E, F) ovarian carcinoma cell lines 36M (■) and SK-OV-3 (□). Normal cells including the HLA-A2⁺ fibroblast cell line GM847 (△) and primary monocytes from 3 HLA-A2⁺ (○, ◇, ▽) and one HLA-A2⁻ healthy donors (□) were not lysed by either (G) CYP239-specific or (H) CYP246-specific CTL. Results of one representative experiment are shown. Similar results were obtained for each of 2 to 6 CTL tested per target.

Fig. 5 is a graph showing the specific lysis of tumor cells pulsed with CYP239 by CYP239-specific CTLs.

Figs. 6A-6C are graphs showing lysis of CYP1B1⁺ HLA-A2⁺ primary lymphoma and acute myeloid leukemia (AML). Two HLA-A2⁺ CYP1B1⁺ follicular lymphoma samples (■ and ●) from lymph node biopsies were lysed by (A) CYP239-specific and (B) CYP246-specific CTL, while no cytotoxicity occurred against an HLA-A2⁻ CYP1B1⁺ FL (□). Experiments were performed from two different normal donors with similar results. (C) CYP239-specific CTL lysed primary HLA-A2⁺ (◆), but not HLA-A2⁻ (◇) AML cells.

Figs. 7A and 7B are each a series of graphs showing the generation of CYP239- and CYP246-specific CTL from cancer patients. (A) CYP239-specific CTL from 4 patients (pt 1-4) and CYP246-specific CTL from pt 3 and pt 4 lysed T2 cells pulsed with the immunizing peptide (■), but not unpulsed T2 cells (□) or T2 cells pulsed with the irrelevant F271 peptide from MAGE-3 (○). (B) The same CYP239- or CYP246-specific CTL lysed the CYP1B1⁺ HLA-A2⁺ myeloma cell lines IM-9 (◆) and U266 (●) but not the CYP1B1⁻ HLA-A2⁻ line HS-Sultan (◇). In two cases, IM-9 cells were not lysed. All experiments shown here were performed twice with similar results.

Fig. 8 is a graph showing that the efficacy of a combination of CYP1B1 and hTERT-specific CTL in a chromium release assay. CYP239- and I540-specific CTL were used individually or in combination against a mixture of T2 cells pulsed with either CYP239 or I540 peptide. Target cells were mixed at a 1:1 ratio using a final number of 5000 cells/well. Numbers shown reflect the number of effector cells added to each well.

Fig. 9 is a graph showing the specific lysis of target cells with CTLs specific for heteroclitic peptides CYP239-19 and CYP239-139.

Fig. 10 is a graph showing the stability of HLA-A2/peptide complexes including the indicated peptides, as determined by TAP-deficient T2 cell assays.

Fig. 11 is a graph showing the stability of HLA-A2/peptide complexes including CYP190 and CYP528, as determined by TAP-deficient T2 cell assays.

Figs. 12A-12C are graphs showing that CYP190-specific CTL lyse peptide-pulsed T2 cells (A), HLA-A2⁺ myeloma cell lines, and HLA-A2⁺ primary ALL cells (C).

Figs. 13A and 13B are graphs showing that CYP190-specific CTL can be generated from cancer patients, such as a (A) prostate cancer patient (HLA-A2⁺), and (B) a multiple myeloma patient (HLA-A2⁺).

Fig. 14 is a graph showing the generation and verification of CYP1B1-specific tetramers including CYP239, CYP246, or a control, Tax 11.

Fig. 15 is a schematic representation of a system to detect CYP1B1 T cells by HLA-A2/peptide tetrameric complexes.

Fig. 16 is a set of graphs showing the detection of CYP1B1-specific CTL in normal HLA-A2⁺ donors.

Fig. 17 is a set of graphs showing the detection of CYP1B1-specific CTL in HLA-A2⁺ multiple myeloma patients.

Detailed Description

We have discovered that cytochrome P450 1B1 (CYP1B1) includes peptides that bind to HLA molecules. Antigen presenting cells (APCs) that present such peptides on their surfaces, in complexes with HLA, can activate

cytotoxic T lymphocytes (CTLs) to specifically lyse cells expressing CYP1B1, in an MHC-restricted fashion. The invention thus provides methods for immunotherapeutic targeting of CYP1B1-expressing cells, such as cancer cells, and methods of monitoring the efficacy of such therapeutic methods.

5 Based on our observations that CYP1B1 is a mediator of dioxin-related effects on tumorigenesis, in combination with searches of public literature databases, such as PubMed, we identified CYP1B1 as a potential universal tumor antigen. It is overexpressed in nearly 100% of human tumors (Murray *et al.*, Cancer Res. 57:3026-3031, 1997), whereas the expression in normal tissue is low
10 and limited to steroidogenic and steroid-responsive tissue (Buters *et al.*, Proc. Natl. Acad. Sci. USA 96:1977-1982, 1999). CYP1B1 is a member of the superfamily of monooxygenases responsible for the metabolic activation of environmental carcinogens. Mice lacking CYP1B1 have a much lower incidence
15 of lymphoma than wild type mice after challenge with polycyclic aromatic hydrocarbons, further implicating that CYP1B1 plays a role in oncogenesis.

T cell mediated anti-tumor immunity

As is noted above, there is considerable evidence that human T cells can specifically lyse tumor cells (Rosenberg, Immunity 10:281-287, 1999). Most
20 attention has been focused on CD8⁺ CTLs as the principle effector cells of antigen-specific anti-tumor immunity. Chief among the recent discoveries that have helped propel clinical efforts has been the characterization of tumor associated antigens (TAAs) (Boon *et al.*, Annual Review of Immunology 12:337-365, 1994). Pioneering studies in the early 1990s demonstrated the
25 existence of human TAAs using patients' CTLs that recognized peptides derived from these antigens (Van Pel *et al.*, Immunological Reviews 145:229-250, 1995; Rosenberg, Immunol. Today 18:175-182, 1997). Although these studies primarily focused on melanoma, TAAs have been subsequently characterized in several other malignancies (Van Pel *et al.*, Immunological Reviews 145:229-250,
30 1995; Rosenberg, Immunol. Today 18:175-182, 1997; Van den Eynde *et al.*, Curr. Opin. Immunol. 9:684-693, 1997), raising the hypothesis that most, if not all,

tumors express antigens that CTL can potentially attack. The demonstration that TAA-specific immune responses can lead to tumor regression has been borne out extensively in animal models (Rosenberg, *Immunity* 10:281-287, 1999). Although the identification of TAAs using patients' CTLs has revitalized the field of T cell immunotherapy, these methods are slow, very expensive, and labor-intensive. Moreover, the strategy relies on the generation of tumor-specific T cell clones *in vitro*, suggesting that only a restricted set of TAAs will be identified by this method. With these limitations in mind, Pfreundschuh and colleagues developed an alternative approach, SEREX (serological identification of antigens by recombinant expression cloning), to identify TAAs (Sahin *et al.*, *Curr. Opin. Immunol.* 9:709-716, 1997). SEREX makes use of patients' antibody responses to tumor-derived genes and this strategy has accelerated the identification of TAAs significantly. Although several T cell-defined TAAs, such as the MAGE genes, have also been identified by SEREX, there is no information available about CTL epitopes for the vast majority of genes in the SEREX database, and, of course, such epitopes are required to activate a CTL response.

Although there is no doubt that the identification of numerous TAAs by CTL-based approaches or SEREX reflects the existence of an anti-tumor immune response, it remains to be determined if these antigens play a role as tumor regression antigens (Sarma *et al.*, *J. Exp. Med.* 189:811-820, 1999). As is mentioned above, most T cell epitopes in TAAs identified by patient CTLs have been demonstrated to be of low MHC binding affinity and/or low MHC/peptide complex stability. Clinical vaccination trials have circumvented this obstacle by utilizing altered peptides with higher MHC binding affinity and higher MHC/peptide complex stability (Rosenberg *et al.*, *Nat. Med.* 4:321-327, 1998). This quality distinguishes TAA-derived peptides from viral peptides that are almost exclusively of high binding affinity and high MHC/peptide complex stability (Feltkamp *et al.*, *Mol. Immunol.* 31:1391-1401, 1994; Sette *et al.*, *J. Immunol.* 153:5586-5592, 1994). The low binding affinity of TAA-derived peptides is likely to be one of the reasons why natural CTL responses against such peptides are not successful for tumor eradication. This is in agreement with the

finding that large numbers of TAA-specific CTLs co-exist with metastatic tumors in melanoma patients (Romero *et al.*, J. Exp. Med. 188:1641-1650, 1998). A recent study has even demonstrated that despite expansion, such CTLs were hyporesponsive, showing reduced cytotoxic and cytokine responses (Lee *et al.*, 5 Nat. Med. 5:677-685, 1999).

To overcome these limitations of currently known TAAs, we have developed methods to identify more universal TAAs, and, in particular, those containing T cell epitopes with high MHC binding affinity and high MHC/peptide complex stability. Such TAAs and MHC-binding peptides thereof can trigger 10 sufficient CTL responses against a broad range of tumor types. Rather than analyzing tumor-derived T cell clones or tumor-specific antibodies derived from patients, an alternative strategy was used, in which TAA and their CTL epitopes are deduced from genes known to be selectively expressed in tumors. By combining bioinformatics to predict peptides that bind to HLA with high affinity, 15 peptide binding analysis, and a powerful *in vitro* T cell expansion system, the cytochrome P450 1B1 (CYP1B1) was identified (see below). This TAA contains at least two peptide epitopes that (1) bind to HLA-A*0201 with high affinity and high MHC/peptide complex stability, (2) are naturally processed and presented by HLA-A*0201 molecules on the cell surface of a panel of tumor cell lines, (3) 20 elicit peptide-specific HLA-restricted CTL responses, and (4) are recognized by such CTL on a wide variety of different tumor histologies.

Deducing CTL epitopes in tumor associated antigens (TAAs): Making use of genomics and proteomics for tumor immunology

25 Current developments in genomics and proteomics suggest that numerous TAA candidate genes can be identified. The Human Genome Project (HGP), the Human Cancer Gene Anatomy Project (CGAP), the SEREX database, and other databases, including literature databases such as PubMed, provide an enormous set of data that can be analyzed to identify genes that fulfill the criteria 30 of universal tumor antigens, as are described above. It is clear that entering the post-genomic era, none of the classical approaches to characterize TAA, including

T cell cloning and testing of T cell clones against expression libraries (Boon *et al.*, Annual Review of Immunology 12:337-365, 1994), is suitable for the analysis of the ever-growing databases to identify a set of universal tumor antigens.

To overcome the limitations of prior methods in determining CTL epitopes, advances in bioinformatics can be applied. First, database mining and integration can be used to identify of universal tumor antigen candidates, which are genes that are expressed at a much higher level in tumor cells than in normal cells. Then, computational methods are used to predict peptides derived from these proteins for high-affinity binding to MHC molecules. The requirements for peptides to bind to class I HLA molecules and to elicit CTL responses have been studied extensively (Rammensee *et al.*, Annual Review of Immunology 11:213-244, 1993; Sidney *et al.*, Immunology Today 17:261-266, 1996). The strength of CD8⁺ CTL responses depends upon the binding affinity of the target peptide to MHC, the peptide-MHC complex stability, and the avidity of T cell receptor (TCR) binding for the peptide complex (Sette *et al.*, J. Immunol. 153:5586-5592, 1994; van der Burg *et al.*, J. Immunol. 156:3308-3314, 1996; Savage *et al.*, Immunity 10:485-492, 1999; Gallimore *et al.*, Eur. J. Immunol. 28:3301-3311, 1998). These factors directly influence the efficiency of peptide loading and the number of peptides expressed on the cell surface (Gallimore *et al.*, Eur. J. Immunol. 28:3301-3311, 1998). The vast majority of viral-derived immunodominant peptides are of high binding affinity and/or peptide-HLA complex stability (Feltkamp *et al.*, Mol. Immunol. 31:1391-1401, 1994; Sette *et al.*, J. Immunol. 153:5586-5592, 1994). Since only a very small portion of peptides can bind to MHC molecules, rapid and accurate methods to identify them, such as those used in the present invention, can expedite the search for CTL epitopes by orders of magnitude.

A great deal of effort has been expended on the development of computational methods to identify peptides that bind strongly to various MHC alleles. It began with the work of Rammensee and colleagues, who identified motifs in peptide sequences that serve as signatures of the MHC molecules to which they bind (Rammensee *et al.*, Immunogenetics 41:178-228, 1995). Motif-

based methods have recently been applied to the identification of CTL epitopes deduced from proteinase 3 (Molldrem *et al.*, *Blood* 88:2450-2457, 1996), MAGE-3 (Nijman *et al.*, *Eur. J. Immunol.* 23:1215-1219, 1993), MUC-1 (Brossart *et al.*, *Blood* 93:4309-4317, 1999), and telomerase (PCT/US99/25438).

5 Typically, only 20% of peptides that carry the motif bind to the respective MHC molecule. The inclusion of "secondary anchor" positions (Ruppert *et al.*, *Cell* 74:929-937, 1993), the so-called extended motif, significantly improves the specificity of motif-based methods, but they are available only for HLA-A*0201 (Ruppert *et al.*, *Cell* 74:929-937, 1993) and HLA-B*3501 (Schönbach *et al.*, *J. Immunol.* 154:5951-5958, 1995). Many other statistically-based computational methods have been developed (for reviews, see, *e.g.*, Hammer, *Curr. Opin. Immunol.* 7:263-269, 1995; Parker *et al.*, *Immunol. Res.* 14:34-57, 1995), including the polynomial method (Gulukota *et al.*, *J. Mol. Biol.* 267:1258-1267, 1997), methods based on neural nets (Gulukota *et al.*, *J. Mol. Biol.* 267:1258-1267, 1997; Brusic *et al.*, *Bioinformatics* 14:121-130, 1998; Brusic *et al.*, *Nucleic Acids Res.* 26:368-371, 1998), a method that assigns a score for each amino acid at each position as determined experimentally *via* single residue substitutions (Hammer *et al.*, *J. Exp. Med.* 180:2353-2358, 1994), and a method developed by Parker *et al.* based on a database of the half-lives of bound

10 15 β2-microglobulin (β2m) in MHC-peptide complexes (Parker *et al.*, *J. Immunol.* 152:163-175, 1994). The method developed by Parker *et al.* assumes that the dissociation of β2m is rate-limited by the dissociation of peptide, so that variation in the microglobulin half-life reflects variation in the peptide half-life. The variation is, in turn, assumed to reflect the variation in the binding affinity of the peptide. A weight matrix is then determined to best reflect the half-lives, assuming that the contribution of one peptide position does not depend on its

20 25 neighboring positions.

Weng and colleagues have recently developed a new statistical method (implemented as a computer program named LPpep; Weng *et al.*, <http://bioinformatics.bu.edu/peptides.html>) to predict strong HLA-A*0201-binding peptides. It determines the contributions for each of the 20

amino acids at each of the positions of a peptide using a linear programming algorithm. When tested on a data set of over 1000 peptides having known binding affinities, LPpep has a higher sensitivity (>0.75) and specificity (> 0.9) than four other available methods.

5

High volume analysis of peptide MHC affinity and MHC/peptide complex stability

The basic principles of peptide binding to MHC molecules have been well established in the field (Rammensee *et al.*, Annual Review of Immunology 11:213-244, 1993; Rothbard *et al.*, Annual Review of Immunology 9:527-565, 1991; Engelhard, Annual Review of Immunology 12:181-207, 1994; Madden, Annual Review of Immunology 13:587-622, 1995; Pamer *et al.*, Annual Review of Immunology 16:323-358, 1998; Rock *et al.*, Annual Review of Immunology 17:739-779, 1999), and numerous assay systems have been developed to analyze the binding of any given peptide to MHC molecules. Binding has been analyzed using intact TAP-deficient cells (Salter *et al.*, EMBO J. 5:943-949, 1986; Schumacher *et al.*, Cell 62:563-567, 1990) and by *in vitro* assays utilizing purified HLA molecules (Ruppert *et al.*, Cell 74:929-937, 1993; Schumacher *et al.*, Cell 62:563-567, 1990; Townsend *et al.*, Cell 62:285-295, 1990). While most assay systems have focused on the maximal binding affinity, it has recently been suggested that the dissociation rate of MHC and peptide (also measured as MHC/peptide complex stability) may be a more important determinant for characterizing a peptide as a dominant T cell epitope (van der Burg *et al.*, J. Immunol. 156:3308-3314, 1996; Busch *et al.*, J. Immunol. 160:4441-4448, 1998; Kammer *et al.*, J. Exp. Med. 190:169-176, 1999).

25

In vitro analysis of CTL responses

The generation of antigen-specific T cells *in vitro* is a classical immunological technique. Antigen-specific T cells can be generated relatively easily if the peptides used to make such cells are: (1) immunodominant, (2) of viral or other non-self origin, (3) expressed at a reasonably high copy number on the cell surface (Porgador *et al.*, Immunity 6:715-726, 1997), and (4) of high

affinity for, and of low dissociation rate (high MHC/peptide complex stability) from, MHC, and if the T cell pool under study has been exposed to the antigen *in vivo* prior to *ex vivo* analysis (recall response). The frequency analysis of peptide-specific T cells by tetramer technology (see below) revealed a 5 significantly higher frequency than earlier assays based on *in vitro* expansion had suggested.

It is therefore apparent that only a fraction of specific CTLs are expanded in classical *in vitro* systems utilizing unstimulated peripheral blood mononuclear cells (PBMC) as antigen presenting cells (McMichael *et al.*, *J. Exp. Med.* 187:1367-1371, 1998). To circumvent these pitfalls, *in vivo* systems 10 utilizing transgenic mice carrying human HLA genes have been introduced (Man *et al.*, *International Immunology* 7:597-605, 1995; Wentworth *et al.*, *International Immunology* 8:651-659, 1996; Alexander *et al.*, *J. Immunol.* 159:4753-4761, 1997). However, these systems are expensive and are not suitable for screening 15 multiple peptide epitopes simultaneously. Making use of new findings in basic immunology, it is possible to optimize further currently available *in vitro* culture technology. The use of an APC instead of PBMC as stimulators is only one example.

We have developed a system that utilizes dendritic cells (DC) for 20 primary activation and CD40-activated B cells (CD40-B) for re-stimulation, thereby mimicking the physiological sequence of events between T cells and APCs during an ongoing immune response (Schultze *et al.*, *J. Exp. Med.* 89:1-12, 1999; Schultze *et al.*, *J. Clin. Invest.* 100:2757-2765, 1997). This system has been 25 successfully used for the identification of T cell epitopes derived from hTERT and the clonal immunoglobulin in B cell malignancies (PCT/US99/25438). From a single blood draw, professional APCs, including DCs and CD40-activated B cells, are generated, and the remaining PBMCs are enriched for CD8⁺ T cells. T cells are primarily stimulated with peptide-pulsed DC, and repeatedly stimulated with peptide-pulsed CD40-B cells. Peptide-specificity and HLA-restriction is 30 analyzed after a total of 2-5 stimulations, depending on the antigen under study. This system is not only very powerful in amplifying rare T cells against

TAA-derived peptides, but has several other advantages: (1) it is relatively cheap compared to transgenic mice, (2) a single blood draw is sufficient to generate all cellular components necessary, and (3) the use of professional APCs for restimulation is superior to PBMC.

5 Classically, the function of CTLs *in vitro* has been defined by cytotoxicity assays using radioactive chromium. Clearly, cytotoxicity analysis is an important component of the characterization of a novel TAA, since tumor cell lysis is the ultimate goal of any TAA-directed immunotherapeutic intervention. However, such assays are not suitable to determine the frequency of peptide-specific CTLs. In addition, the sensitivity of cytotoxicity assays to identify very small numbers of specific CTLs is insufficient. To detect very low numbers of specific CTLs and to determine their frequency, two new technologies, namely the tetramer technology (Altman *et al.*, *Science* 274:94-96, 1996) and cytokine ELISPOT analysis (Herr *et al.*, *J. Immunol. Methods* 203:141-152, 1997), have been developed and applied to tumor immunology. In particular, tetramers have been suggested as a tool to enrich CTL lines for peptide-specific CTL (Dunbar *et al.*, *Curr. Biol.* 8:413-416, 1998; Yee *et al.*, *J. Immunol.* 162:2227-2234, 1999; Valmori *et al.*, *Cancer Res.* 59:2167-2173, 1999). Currently, the tetramer technology is still technically demanding and it is not possible to generate numerous tetramers in small quantities to screen peptide-specific CTL responses against a larger set of unknown peptides. For this purpose, cytokine ELISPOT is more suitable (Herr *et al.*, *J. Immunol. Methods* 203:141-152, 1997).

25 Experimental Results

The dioxin-inducible cytochrome P450 1B1 (CYP1B1)

Using the methods described above (also see PCT/US99/25438), we identified the dioxin-inducible cytochrome P450 1B1 (CYP1B1) as a potential TAA. A list of peptides predicted to bind to all HLA alleles available are listed in the Sequence Appendix. The prediction was carried out using three different algorithms that are freely available on the Internet:

<http://engpub1.bu.edu/LPpep-cgi/peptide2.cgi>
<http://www.uni-tuebingen.de/uni/kxi/>
http://bimas.dcrt.nih.gov/molbio/hla_bind/

Analysis of the CYP1B1 sequence by two independent prediction algorithms
5 (BIMAS and LPpep, see Experimental Methods, below) revealed two peptides
(CYP239 and CYP246) predicted to bind to HLA-A*0201, the most common
HLA allele (Table 1). These peptide sequences are unique in the public gene
databases and in particular are not found within any other member of the
cytochrome P450 family. (Also see below for additional CYP1B1 peptides (e.g.,
10 CYP190 and CYP528) identified according to the invention.)

Peptide binding of CYP1B1 derived peptides

Binding of both peptides to HLA-A2, as well as their complex stability,
was determined using a cellular assay employing TAP-deficient T2 cells (Table 1;
15 PCT/US99/25438). Both peptides stabilized HLA-A2 molecules on the surface of
T2 cells to a similar extent as a positive control peptide (F271) derived from the
tumor antigen MAGE-3 (Nijman *et al.*, Eur. J. Immunol. 23:1215-1219,1993),
which is known to bind HLA-A2 with high affinity. In particular, T2 cells were
incubated with peptide in serum-free medium for up to 18 hours, harvested,
20 washed, and subsequently stained with FITC-labeled anti-HLA-A2 mAb BB7.2
(maximum peptide binding). Increase in fluorescence intensity was determined as
a function of peptide binding. For analysis of complex stability, T2 cells were
cultured in serum-free media for an additional 2, 4, 6, or 24 hours, and
subsequently analyzed for HLA-A2 expression by flow cytometry. As is shown
25 in Fig. 1, the MAGE-3-derived peptide, which induces CTL responses in the
majority of all normal donors, demonstrated high binding affinity and complex
stability. Although both CYP1B1-derived peptides bound to HLA-A2, CYP246
showed a significantly lower complex stability than CYP239 and MAGE-3.
Moreover, attempts to induce CTL responses were successful in 13/15 donors
30 against CYP239, but only 4/9 donors for CYP246. Our data further show that

complex stability might be a more important factor than binding affinity for the likelihood to generate peptide-specific CTL responses.

5
TABLE 1
Binding of CYP1B1 and control peptides to human HLA-A*0201

	sequence	BIMAS ¹	LPpep ²	binding affinity ³ [FI]
10	SLVDVMPWL	1108	2.88	3.8
	WLQYFPNPV	1216	6.23	3.4
	FLWGPRALV	2655	7.63	3.2

15 1 Peptide prediction at BIMAS (BioInformatics & Molecular Analysis Section): scores for predicted binding are calculated as half-life of MHC/peptide complexes (peptides with scores > 500 were chosen as potential candidates).

2 2 LPpep (peptide prediction at Boston University): scores are predicted as arbitrary ln(IC₅₀) concentrations (peptides with scores < 7 were chosen as potential candidates).

20 3 Mean fluorescence with peptide / mean fluorescence without peptide - 1. Results representative of 4 experiments.

Peptide-specific killing

To test whether CYP239 and CYP246 reactive T cells are present in the human T cell repertoire, CTL lines were generated *ex vivo* by repetitive stimulation with peptide pulsed autologous APC. CTL specific for CYP239 were induced from peripheral blood mononuclear cells (PBMC) in 11 of 13 healthy HLA-A2⁺ donors (Fig. 2A). These CTL specifically lysed T2 cells pulsed with CYP239 peptide, while no cytotoxicity occurred against unpulsed T2 cells or T2 cells pulsed with the F271 peptide from MAGE-3. CYP246 specific CTL were generated in 4 of 10 healthy HLA-A*0201⁺ donors (Fig. 2B). HLA-A2 restriction was demonstrated using autologous and HLA-A2 mismatched CD40-activated B cells (CD40-B) as targets (Figs. 2C and 2D). CYP239-specific CTL lysed autologous CD40-B pulsed with CYP239, but not allogeneic HLA-A2- CD40-B pulsed with CYP239 (Fig. 2C). Similar results were obtained for CYP246-specific CTL (Fig. 2D).

Experiments titrating the concentration of peptide onto the CD40-activated B cells before the cytotoxicity assay further support the peptide-specificity of the CTL generated against the CYP239 peptide. Comparing the data with published data in the literature the cell line tested in this experiment 5 is of intermediate avidity. Alternatively, the cell line contains both high and low avidity CTL and the curve represents the sum of the actions of these CTLs (Fig. 3).

For both CYP239 and CYP246 CTL, specificity was further demonstrated using peptide/MHC tetramers (Fig. 2E). Frequency analysis using CYP239 10 tetramers demonstrated that 1.4-2.4% of all CD8⁺ T cells recognized the CYP239 peptide, a percentage comparable to previously published data for gp100 specific (Yee *et al.*, J. Immunol. 162:2227-2234, 1999) or proteinase-3 specific CTL lines (Molldrem *et al.*, Cancer Res. 59:2675-2681, 1999). CYP246-specific CTLs were detected with CYP246 tetramer, but the frequency of specific CTL was lower 15 (0.47%). To further confirm peptide-specific cytotoxicity, CYP239 tetramer-positive CTL were sorted and expanded using phytohemagglutinin (PHA), IL-7, IL-2, and irradiated allogeneic PBMC. These CTL lysed T2 cells pulsed with CYP239 at extremely low E:T ratios, but not unpulsed T2 cells or T2 cells pulsed 20 with an irrelevant HLA-A2 binding peptide (Fig. 2F). Thus, CYP1B1 contains at least two HLA-A*0201 binding peptides, and T cells recognizing these peptides are present in the T cell repertoire of healthy donors.

CYP1B1 specific CTL lyse CYP1B1 expressing tumors in an HLA-A2 restricted fashion

25 Although peptide-specificity of CTL is demonstrated by lysis of peptide-pulsed target cells, it is important to show that tumor cells themselves process and present the peptide in the groove of their MHC molecules (Yee *et al.*, J. Immunol. 162:2227-2234, 1999). We approached this question by using a panel of HLA-A2⁺ and HLA-A2⁻ tumor cell lines that all express CYP1B1 protein. CYP239- and 30 CYP246-specific CTL from healthy donors were then screened for cytotoxicity (Figs. 4A-4H). CYP239 CTL (Fig. 4A) and CYP246 CTL (Fig. 4B) showed

specific lysis of HLA-A2⁺ melanoma cell line K029, but not HLA-A2⁻ SK-MEL-2 cells. Similarly, the HLA-A2⁺ myeloma cell lines IM-9 and U266 were lysed by CYP239 CTL (Fig. 4C) and CYP246 CTL (Fig. 4D), while the HLA-A2⁻ myeloma HS-Sultan cell line was not killed. Finally, specific cytotoxicity by 5 CYP239 CTL (Fig. 4E) and CYP246 CTL (Fig. 4F) was observed against the HLA-A2⁺ ovarian carcinoma cell line 36M, but not the HLA-A2⁻ line SK-OV-3. These data show that CYP1B1 derived peptides are naturally processed and presented by tumor cell lines of different tissue origin.

Since CYP1B1 expression has been reported in fibroblasts (Eltom *et al.*, 10 *Carcinogenesis* 19:1437-1444, 1998) and monocytes (Baron *et al.*, *Biochem. Pharmacol.* 56:1105-1110, 1998), we analyzed an HLA-A2⁺ fibroblast cell line (GM847) and primary peripheral blood derived monocytes from four healthy donors as targets for CYP1B1-specific CTL. Western blot analysis showed that of these normal cells express low or absent levels of CYP1B1. As is shown in 15 Figs. 4G and 4H, CYP239 and CYP246-specific CTL failed to lyse these normal targets. In contrast, CD40-activated B cells strongly express CYP1B1 protein (detected by Western blot), but these normal cells were not lysed by CYP239- or CYP246-specific CTL (Figs. 2C and 2D), suggesting that there is a differential expression of CYP1B peptides on tumor cells.

20

Methods to improve killing of tumor cell lines

The experiments described so far suggest that CYP239 peptide is most likely expressed at low levels on tumor cell MHC. Alternatively, tumor cells could be more resistant to CTL-mediated lysis. To address these issues and to 25 determine whether the increase of peptide on the cell surface of tumor cells would lead to increase killing of the tumor cells, tumor cells were pulsed with the specific peptide before they were used in chromium release assays. We could demonstrate that peptide-pulsing of tumor cells significantly increased killing of the target cells, suggesting that the level of naturally expressed CYP239 peptide is 30 low on the tumor cells, however, that these cells can be readily killed once the level of peptide is increased. This also suggests that any methodology to increase

the expression of CYP1B1-derived peptides on the cell surface will make the tumor cell a susceptible target for CYP1B1-specific CTLs (Fig. 5).

Lysis of primary HLA-A2⁺ follicular lymphoma cells

5 CYP1B1-specific CTLs were then evaluated for cytotoxicity against primary tumor tissue. Because CYP1B1^{-/-} mice demonstrate a significantly reduced incidence in carcinogen-induced lymphomas (Buters *et al.*, Proc. Natl. Acad. Sci. U.S.A. 96:1977-1982, 1999), we chose to study human primary follicular lymphoma (FL) as a model tumor target for CYP1B1 specific CTL.

10 Tumor cells from two HLA-A2⁺ FL samples and one HLA-A2⁻ FL sample were found to be CYP1B1⁺ as assessed by Western blot analysis. Using these target cells, we found that CTL lines generated against CYP239 or CYP246 were cytotoxic for the HLA-A2⁺ FL, while no killing of the HLA-A2⁻ FL was observed (Figs. 6A and 6B). We also demonstrated lysis of HLA-A2⁺ primary acute

15 myeloid leukemia (AML) cells, but not HLA-A2⁻ primary AML cells by CYP239 CTL (Fig. 6C). These data show that both CYP1B1-derived peptides are processed and presented by HLA-A2 on primary tumor cells and that HLA-A2 restricted CYP1B1 specific CTL from healthy donors can recognize and kill these target cells.

20

Generation of CYP1B1-specific CTL from patients with multiple myeloma

Similar to experiments described for healthy donors, we next attempted to generate CYP1B1-specific CTL from peripheral blood of cancer patients. HLA-A2⁺ patients with multiple myeloma (n=3) or follicular lymphoma (n=1) (Table 2) were tested for *ex vivo* generation of CYP239 (n=4) or CYP246 (n=2) specific CTL. Generation of all cellular components of our *ex vivo* system (*i.e.*, dendritic cells, CD40-B, and CTL), as well as expansion of CTL to CYP239 and CYP246 were similar to results obtained for healthy donors. Using peptide-pulsed T2 cells as targets, we demonstrated CYP239-specific CTL in all four patients (Fig. 7A). Due to lower numbers of PBMC available, CYP246-specific CTL cultures were only initiated in patients 3 and 4. CYP246-specific CTLs were

detected in both patients. These patient-derived lines showed tumor-specific lysis of HLA-A2⁺ myeloma cell lines U266 and IM-9, but not the HLA-A2⁻ myeloma cell line HS-Sultan (Fig. 7B). Because autologous tumor cells were not available from these patients, we tested the same FL samples described above as primary tumor targets. CYP239-specific CTL from patient 1 lysed both HLA-A2⁺ FL samples but not the HLA-A2⁻ (18% vs. 0% at an E:T ration of 30:1).

TABLE 2

patient	age	sex	disease	stage	prior treatment	CTL induction	
						CYP239	CYP246
1	41	f	Multiple Myeloma	I A	none	yes	ND
2	47	f	Multiple Myeloma	II A	none	yes	ND
3	40	m	Multiple Myeloma	III A	High-Dose Dexamethasone, discontinued >30d prior to leukapheresis	yes	yes
4	29	m	Non Hodgkin's Lymphoma (Follicular Lymphoma)	III A	none	yes	yes

Patient characteristics, prior treatment, and CTL induction

ND = not determined

10

Combining CYP1B1- and hTERT-specific CTL

We next analyzed the combination of CYP1B1-specific CTL with hTERT-specific CTL (Vonderheide *et al.*, *Immunity* 10:673-679, 1999). To 15 normalize for equal susceptibility to T-cell mediated lysis, we used a mixture (1:1 ratio) of T2 cells pulsed with either CYP239 or I540 hTERT peptide (Vonderheide *et al.*, *Immunity* 10:673-679, 1999) as a model for heterogeneous antigen expression. Equal ⁵¹Cr labeling of both T2 cell populations was assured. Under these conditions, it is expected that either CTL line alone can only lyse a 20 maximum of 50% of the target cell population while the combination if effective has the potential to kill >50% of all cells (Janeway, *Immunobiology: The Immune System in Health and Disease* (Garland Publishing c/o Taylor & Francis, Inc.,

New York, 1999), p. 297). This is true for specific lysis regardless of the E:T ratio used. As postulated, the combination of CYP239- and I540-specific CTL was superior to each CTL line alone, achieving specific lysis of >50% (Fig. 8). Similar observations were made in independent experiments using CTL generated from two different donors. We also analyzed the effect of combined CYP1B1 and hTERT CTL on the HLA-A2⁺ tumor cell line IM-9, which expresses both antigens. In two experiments, we observed additive lysis of CYP239- and I540-specific CTL across a range of E:T ratios. These data demonstrate the potential of enhancing antigen-specific T cell immunity by targeting multiple antigens, such as CYP1B1 and hTERT.

Use of heteroclitic peptides

To improve immunogenicity of CYP1B1 derived peptides, we designed heteroclitic peptides optimized for binding affinity to MHC. We have already shown that CTL generated against the CYP239 wild type peptide can recognize and lyse target cells pulsed with the heteroclitic peptide CYP239-19 equally well, while CTL generated with CYP239 do not recognize CYP239-139. These data show that despite similar binding, the change of a third amino acid does not allow for recognition by CTL specific for CYP239. Most likely, the amino acid change induced a change in the three dimensional structure of the peptide not allowing TCR activation (Fig. 9). To design heteroclitic peptides with higher binding affinity, we used an algorithm available on the Internet (<http://engpub1.bu.edu/LPpep-cgi/peptide3.cgi>). Two heteroclitic peptides to the immunogenic peptide CYP239 have been designed as examples to improve binding affinity, complex stability, and, potentially, immunogenicity (Table 3).

TABLE 3
Examples of Heteroclitic Peptides Optimized for Binding to HLA-A*0201
heteroclitic 9mers

position	peptide	nmer	Parker score	Zhiping score	T2 assay result
292	YLYAFILSV	9	8948.1	-0.99	n.d.
344	YLYTRYPDV	9	1535.7	0.7	n.d.
380	YLYAFLYEV	9	8948.1	-3.51	n.d.
246	YLYYFPNPV	9	3890.5	-0.27	n.d.
239 (1, 3, 9)	YLYDVMPWV	9	53099.7	-3.42	2.00
239 (1, 9)	YLVDVMPWV	9	16593.6	-0.85	2.16
239 (1, 3)	YLYDVMPWL	9	16309.2	-1.76	n.d.
239 (3, 9)	SLYDVMPWV	9	11543.4	-1.35	n.d.
239 (1)	YLVDVMPWL	9	5096.6	0.81	n.d.
239 (9)	SLVDVMPWV	9	3607.3	1.22	n.d.
239 (3)	SLYDVMPWL	9	3545.5	0.31	n.d.

5

Peptide binding of heteroclitic CYP239 peptides

The T2 assay described above was used to determine binding and dissociation rate of heteroclitic peptides engineered for optimal binding to HLA molecules. Two heteroclitic peptides to CYP239 were tested and shown to have higher peptide/MHC-complex stabilities, as is shown in Table 4. While the control peptide MAGE-3 and the CYP239 peptide showed no significant binding at 24 hours (0.14 resp. 0.12), both heteroclitic peptides still bound to HLA-A*0201 (0.72 resp. 0.73).

15

TABLE 4
Examples of heteroclitic peptides optimized for binding to HLA-A*0201

time post-pulsing [hours]		0	2	4	6	
MAGE-3	FLWGPRALV	1.88	1.41	0.93	0.77	0.14
CYP239	SLVDVMPWL	1.91	1.37	0.78	0.58	0.12
CYP239-19	YLVDVMPWV	2.16	1.57	1.31	1.13	0.72
CYP239-139	YLYDVMPWV	2.00	1.51	1.24	1.16	0.73

The following Tables 5 and 6 show predicted mutations to improve HLA-A2
5 binding of CYP1B1 239 and CYP1B1 246.

TABLE 5
Predict Mutations to Improve HLA-A2 Binding CYP239

5 Under each position, a list of possible amino acid mutations is given, followed by the change in the predicted $\ln(\text{IC50})$ produced by the mutation with respect to the original peptide's score.

POSITION								
1	2	3	4	5	6	7	8	9
K (0.17)	*	A (1.31)					A (0.60)	
M (2.03)		C (1.35)					I (1.36)	
F (0.60)		G (0.57)					V (1.66)	
Y (2.07)		H (0.78)						
		L (1.63)						
		M (2.00)						
		F (1.40)						
		P (0.19)						
		S (0.55)						
		W (1.38)						
		Y (2.57)						

* indicates best amino acid is already present

Original peptide: SLVDVMPWL, predicted $\ln(\text{IC50}) = 2.88$
 Top scoring peptide under given constraints: YLYDVMPWW, predicted $\ln(\text{IC50}) = -3.42$

TABLE 6
Predict Mutations to Improve HLA-A2 Binding CYP246

Under each position, a list of possible amino acid mutations is given, followed by the change in the predicted $\ln(\text{IC50})$ produced by the mutation with respect to the original peptide's score.

POSITION								
1	2	3	4	5	6	7	8	9
A (1.53)	*	A (1.50)						*
R (1.08)		D (0.10)						
N (0.33)		C (1.54)						
C (0.88)		G (0.76)						
G (1.39)		H (0.97)						
L (0.92)		I (0.16)						
K (1.84)		L (1.82)						
M (3.70)		M (2.19)						
F (2.27)		F (1.59)						
S (1.67)		P (0.38)						
T (0.94)		S (0.74)						
Y (3.74)		W (1.57)						
V (1.21)		Y (2.76)						
		V (0.19)						

* indicates best amino acid is already present

Original peptide: WLQYFPNPV, predicted $\ln(\text{IC50}) = 6.23$
 Top scoring peptide under given constraints: YLYYYFPNPV, predicted $\ln(\text{IC50}) = -0.27$

10

Identification of additional HLA-A2 binding epitopes from CYP1B1

Binding studies were carried out to characterize additional CYP1B1-derived peptides that are predicted to bind to HLA-A2. Table 7, below, shows the 15 sequences of additional peptides that are predicted to bind to HLA-A2.

TABLE 7

Predicted binding of epitopes to HLA-A2
Nonamers predicted to bind to HLA-A*0201

position	peptide	Parker		LP pep		SYFPEITHI	
		score	rank	score	rank	score	rank
25	LLLSVLATV	1006	3	3.54	4	32	1
88	RLGSCPPIVV	29	18	4.61	6	20	31
190	FLDPRPPLTV	128	11	6.52	15	26	5
239	SLVDVMPWL	1108	2	2.88	2	24	9
246	WLQYFPNPV	1216	1	6.23	12	21	22
292	MMDAFILSA	21	19	3.31	3	20	29
344	LLFTRYPDV	656	4	4.69	7	24	7
377	NLPYVLAFL	270	8	7.1	21	25	6
380	YVLAFLYEA	65	14	1.56	1	20	27
479	QLFLFISIL	283	6	5.66	9	26	4
528	LLDSAVQNL	33	16	4.08	5	26	3

Table 1a

Decamers predicted to bind to HLA-A*0201

position	peptide	Parker		LP pep		SYFPEITHI	
		score	rank	score	rank	score	rank
24	LLLLSVLATV	1006	1	4.55	5	24	1
88	RLGSCPPIVL	20	22	3.08	2	26	3
343	LLLFTRYPDV	656	2	5.6	9	343	7
477	KMQLFLFISI	50	13	1.29	1	19	31
479	QLFLFISILA	18	24	3.86	3	15	67
486	ILAHQCDFRA	49	14	3.87	4	18	36

Table 1b

5

Peptides were pulsed onto TAP-deficient T2 cells, and the maximum binding and the stability over time were assessed by flow cytometry. As is shown in Fig. 10, CYP190 and CYP528 show the longest half-life on the cell surface. Additional experiments were carried out to characterize these peptides, in particular, CYP190. As is shown in Fig. 11, further binding studies using TAP-deficient T2 cells showed that CYP190/A2 complexes can be detected as long as 24 hours after peptide withdrawal. Moreover, as is shown in Figs. 12A-12C, CYP190-specific CTL can be generated from normal HLA-A2⁺ donors, and these CTL can lyse peptide-pulsed T2 cells (Fig. 12A), HLA-A2⁺ myeloma cell lines (Fig. 12B), and HLA-A2⁺ primary ALL cells (Fig. 12C). In addition, as is shown

in Figs. 13A and 13B, CYP190-specific CTL can be generated from HLA-A2⁺ cancer patients (Fig. 13A, prostate cancer patient, and Fig. 13B, multiple myeloma patient), and show specific lysis.

We also identified HLA-A3 binding epitopes from CYP1B1. Using the 5 BIMAS server, for example, we identified the peptides shown in Table 8, in which the positive control is a peptide derived from influenza A.

10 **TABLE 8**
Peptides predicted to bind to HLA-A3 (BIMAS server)

rank	position	sequence	score
10mers			
1	508	GLTIKPKSFK	90
2	445	FLDKDGLINK	60
3	450	GLINKDLTSR	27
9mers			
1	150	SMMRNFFTR	54
2	408	SVLGYHIPK	27
positive control	NP265	ILRGGSVAHK	90

15 As is shown in Table 9, these peptides were tested in a binding assay to T2 cells transfected with HLA-A3 (NP265= positive control from influenza A). These studies showed that CYP408, CYP445, and CYP150, which are not homologous to other cytochrome P450 isoenzymes, repeatedly bound to HLA-A3.

TABLE 9
Binding assay of peptides to T2 cells transfected with HLA-A3

peptide	FI class I	FI
PBS	15.3	
NP265	19.4	0.27
CYP508	16.4	0.07
CYP408	16.9	0.10
CYP445	19.5	0.27
CYP450	16.8	0.10
CYP150	17.2	0.12
Flu-MP58	34.8	1.27

5

In further studies, we detected CYP1B1 reactive T cells in HLA-A2+ normal donors HLA-A2+ cancer patients (Fig. 14). Specific binding of tetramers with CYP239 and CYP246 peptides was confirmed on T cell lines generated 10 against the respective peptide. No binding could be detected on T cells generated against an irrelevant peptide. A tetramer containing a peptide from HTLV was used as a negative control.

We also devised a system for detecting CYP1B1-specific T cells by HLA-A2/peptide tetrameric complexes, as is illustrated in Fig. 15. CD8⁺ 15 T cells from normal HLA-A2⁺ myeloma patients (n=10) were isolated and analyzed with HLA-A2/peptide tetrameric complexes directly *ex vivo* and after a 10 day *in vitro* restimulation period with peptide, cytokines, and irradiated PBMC. Viral peptides were used as positive (influenza A, EBV) and negative (HTLV Tax) controls.

As is shown in Fig. 16, T cells from HLA-A2+ healthy donors (n=8) were stained with CYP239 and CYP246 tetramers directly *ex vivo* and 10 days after *in vitro* restimulation with CYP239 or CYP246 peptides. The level of detection on day 10 is at 0.05% as determined from background staining of HLA-A2⁻ donors. No expansion of CYP239-specific T cells was detected in healthy donors on day 25 10 (mean 0.022% \pm 0.018%). CYP246-specific T cells were detected in 2 healthy donors with one rising to 0.5% (mean 0.032% \pm 0.022%).

As is shown in Fig. 17, T cells from HLA-A2+ multiple myeloma patients (n=10) were stained with CYP239 and CYP246 tetramers directly *ex vivo* and 10 days after *in vitro* restimulation with CYP239 or CYP246 peptides. The level of detection on day 10 is at 0.05% as determined from background staining of HLA-
5 A2- donors. 4 patients showed T cells reactive against CYP239 >0.05% on day 10 (mean 0.068% \pm 0.055%), whereas 5 patients showed reactivity against CYP246 (mean 0.098% \pm 0.080%).

Table 10 shows the sequence of CYP1B1 and the sequences of CYP1B1 peptides that were identified by LPEP analysis as having binding affinity for
10 HLA-A2.

TABLE 10
Identify HLA-A2 Binding Peptide Fragments. CYP1B1

	Input Sequence:
5	MGTSLSPNDPWPLNPLSIQQTLLLLSVLATVHVGQRLRQRRRQLRSAPPGPFAWPLIGNAAA VGQAAHLSFARLARRYGDVFQIRLGSCPIVVLNGERAIIHQALVQQGSAFADRPFAFASFRVVSGGR SMAFGHYSEHWKVQRAAHSMMRNFFTRQPRSQRQVLEGHVLSEARELVALLVRGSADGAFLDP RPLTVVAVANVMSAVCFGCRYSHDDPEFRELLSHNEEFGRTVGAGSLVDVMPWLQYFPNPVRTV FREFEQLNRNFSNFI L DKFLRHCESLRPGAA PRDMMDA FILSAEKKAAGDSHGGARLDLENVPA
10	TITDIFGASQDTLSTALQWLLLFTRYPDVQTRVQAELDQVVGDRRLPCM GDQPNLPYVLAFLYE AMRFSSFVPTVTIPHATTANTSVLGYHIPKDTVVFVNQWSVNHDPLKWP NPENFDPARFLDKDGLI NKDLTSRVMIFSVGKRR CIGEELSKMQLFLFISILA HQCDFRANPNEPAKM NFSYGLTIKPKSFKV N VTLRESMELL D SAVQNLQAKETCQ
15	Listed below are 9-residue peptides predicted to bind to the HLA-A2 allele with a $\ln(\text{IC50}) < 8$. The first entry represents the location in the original sequence of the first amino acid of that peptide. Following the location is the peptide, for which the predicted $\ln(\text{IC50})$ is given as the third entry.
20	22 TLLLLLSQL 7.08 23 LLLLLSVA 7.71 24 LLLLLSVLAT 6.05 25 LLLLLSVLATV 3.54 55 FAWPLIGNA 5.11 88 RLGSCPIVV 4.61
25	95 VVVLNGERA 6.58 190 FLDPRPLTV 6.52 200 AVANVMSAV 6.14 239 SLVDVMPWL 2.88 246 WLQYFPNPV 6.23
30	292 MMDA FILSA 3.31 312 GARLDLEN V 7.87 314 RLDLEN VPA 6.27 322 ATITDIFGA 6.74 334 TLSTALQWL 6.64
35	344 LLFTRYPDV 4.69 377 NLPYVLAFL 7.10 380 YVLAFLYEA 1.56 381 VLAFLYEAM 6.09 394 FVPV TIPHA 7.03
40	419 VVFVNQWSV 7.35 479 QLFLFISIL 5.66 487 LAHQCDFRA 7.54 510 TIKPKSFKV 7.60 528 LLDSAVQNL 4.08
45	Listed below are 10-residue peptides predicted to bind to the HLA-A2 allele with a $\ln(\text{IC50}) < 8$.
50	4 SLSPN DPWPL 5.26 20 QTLL LLLSV 6.75 21 TT LLLLS SVL 7.01 22 T LLLLS SVA 5.18 23 L LLLLS VLAT 7.36 24 L LLLS VLATV 4.55 26 L LSV LATVHV 5.86 55 88 RLGSC PIVVL 3.08 190 FLDPR PLTVV 7.88 199 VAVAN VMSAV 7.87 234 TVGAG SLVDV 7.73

255	RTVFREFEQL	7.72
334	TLSTALQWLL	5.85
336	STALQWLLLL	5.96
343	LLLFTRYPDV	5.60
5	380 YVLAFLYEAM	5.54
	388 AMRFSSFVPV	7.39
	418 TVVFVNQWSV	6.72
	477 KMQLFLFISI	1.29
	479 QLFLFISILA	3.86
10	486 ILAHQCDFRA	3.87
	494 RANPNEPAKM	7.06
	502 KMNFSYGLTI	7.12

15 The following Experimental Methods were used to obtain some of the Experimental Results set forth above.

Experimental Methods

Donor and Patient Samples

20 Peripheral blood from healthy blood donors and cancer patients (Table 2) was obtained by leukapheresis and peripheral blood mononuclear cells (PBMC) were purified by Ficoll-density centrifugation (Schultze *et al.*, J. Clin. Invest. 100:2757-2765, 1997). Primary NHL and AML samples were obtained from discarded specimens. Leukapheresis products and tumor tissue were obtained following informal consent and approval by our institute's Review Board.

Cell Lines

The melanoma cell line K029 was a kind gift of Dr. G. Dranoff (Dana-Farber Cancer Institute, Boston). The fibroblast cell line GM847 was a kind gift of Dr. W. Hahn (Whitehead Institute of Biomedical Research, Cambridge). The 36M ovarian carcinoma cell line was a kind gift of Dr. S. Cannistra (Beth Israel Deaconess Hospital, Boston). The TAP-deficient T2 cell line; the multiple myeloma cell lines U266, IM9, and HS-Sultan; the melanoma cell line SK-MEL-2; and the ovarian carcinoma cell line SK-OV-3 were obtained from the American 35 Type Culture Collection (ATCC; Manassas, VA).

Peptides

The peptides CYP239 (SLVDVMPWL; SEQ ID NO:1) and CYP246 (WLQYFPNPV; SEQ ID NO:2) from CYP1B1, the I540 peptide from hTERT (ILAKFLHWL), the RT-pol476 (ILKEPVHGV) peptide from HIV, the HTLV-5 TAX11 (LLFGYPVYV), and the peptide F271 (FLWGPRALV) derived from MAGE-3 were purchased from Sigma Genosys Biotechnologies (The Woodlands, TX).

Peptide Prediction

10 Binding of peptides to HLA molecules can be predicted for the most common HLA alleles by computational methods (Parker *et al.*, *J. Immunol.* 152:163-75, 1994; Gulukota *et al.*, *J. Mol. Biol.* 267:1258-67, 1997). To increase specificity of peptide prediction we used two independent algorithms: a matrix algorithm available on the BIMAS (BioInformatics & Molecular Analysis Section at the NIH) web site (Parker *et al.*, *J. Immunol.* 152:163-75, 1994) and a linear programming algorithm (LPpep) at Boston University (Z. Weng). BIMAS predicts for the half-life of peptides bound to class I molecules, while LPpep predicts an arbitrary half inhibitory concentration (IC₅₀) in competition with a labeled reference peptide. The output value is listed as ln(IC₅₀).

20

*HLA-A*0201 binding assay*

TAP-deficient T2 cells were pulsed with 40 µg/ml of peptide and 3 µg/ml of β2-microglobulin (Sigma, St. Louis, MO) for 18 hours in serum-free IMDM (Life Technologies, Rockville, MD) at 37°C. Cells were washed three times in serum-free IMDM and HLA-A*0201 expression was measured by flow cytometry using FITC-conjugated mAb BB7.2 (ATCC). Increase of HLA-A2 expression on T2 cells reflects stabilization of MHC complexes by the addition of exogenous peptides and was quantified using the fluorescence index (FI = (MFI_{peptide pulsed T2} / MFI_{unpulsed T2}) - 1).

30

Western blot analysis

CYP1B1 expression was determined in microsomal cell fractions. Microsomal protein was isolated by differential speed centrifugation. Cells were harvested, washed, and resuspended in hypotonic buffer. After mechanical 5 homogenization high-density particles were pelleted by centrifugation for 20 minutes at 15,000g. The supernatant was collected and centrifuged for 1 hour at 180,000g. The pellet was resuspended in TEDG buffer, and 100 µg of microsomal protein was separated by SDS-PAGE and transferred to nitrocellulose membrane. Western blot for CYP1B1 was performed according to the 10 manufacturer's recommendations (Gentest, Woburn, MA). Bands were visualized by enhanced chemiluminescent detection (NEN Life Science Products, Boston, MA).

Generation of CTL

15 CTL were generated as previously described (Vonderheide *et al.*, Immunity 10:673-679, 1999), CD8⁺ T cells (>80% CD8⁺, >95% CD3⁺, <2.0% CD4⁺, and <5% CD56⁺) were isolated from PBMC by negative selection using magnetic beads. B cells were activated via CD40, and DC were prepared from peripheral blood monocytes with IL-4 and GM-CSF (Schultze *et al.*, J. Clin. Invest. 20 100:2757-2765, 1997). DC were harvested after 7 days, pulsed with peptide (40 µg/ml) and β2-microglobulin (3 µg/ml) for 2 hr at 37°C, irradiated (33 Gy), and added to autologous CD8⁺ T cells at a T:DC ratio of 20:1 in RPMI media supplemented with 10% human AB serum, 2 mM glutamine, 15 µg/ml gentamicin, 20 mM HEPES, and 15 ng/ml IL-7 (Endogen, Woburn, MA). At day 25 7 and weekly thereafter, T cell cultures were harvested and restimulated with irradiated (33 Gy), peptide-pulsed (10 µg/ml) autologous CD40-activated B cells. IL-2 (50 U/ml; Chiron Corp, Emeryville, CA) was introduced on day 8 and replenished as needed every 3–4 days. Flow cytometry was performed as described (Schultze *et al.*, J Clin. Invest. 100:2757-2765, 1997). Assessment of 30 cytotoxic effector function and tetramer analysis were performed with CTL cultures always >90% CD3⁺/CD8⁺, <5% CD4⁺, and <5% CD56⁺.

Cytotoxicity Assay

To assess cytolytic function CTL lines were used after at least four antigenic stimulations in standard ^{51}Cr release assays as previously described (Vonderheide *et al.*, *Immunity* 10:673-679, 1999). Percent specific lysis was calculated from cpm of (experimental result - spontaneous release)/(maximum release - spontaneous release) $\times 100\%$. Monocytes as targets were isolated from PBMC by RosetteSep[®] (Stem Cell Technologies, Vancouver) following the manufacturer's recommendations.

10

Tetramer analysis

Tetrameric A2/peptide complexes with CYP239, CYP246, and TAX11, an immunogenic peptide derived from HTLV-1, were synthesized essentially as described (Altman *et al.*, *Science* 274: 94-96, 1996) and conjugated to ALEXA-488 (Molecular Probes, Eugene, OR). For staining of CTL lines, cells were incubated with the tetramer and CD8-PE (Beckman Coulter, Fullerton, CA) for 30 minutes at room temperature. Tetramers were also used to sort CYP239-specific CTL. Tetramer sorted CTL were expanded by mitogen stimulation as described (Valmori *et al.*, *Cancer Res.* 59:2167-2173, 1999).

20

Use*Use of universal tumor associated antigens in therapeutic methods*

As is discussed above, the invention provides methods for preventing or treating conditions associated with excessive cell proliferation and expression of CYP1B1, such as cancer.

Examples of conditions that can be prevented or treated using the methods of the invention, include, for example, all cancers, *e.g.*, melanoma, lymphoma, carcinoma, sarcoma, multiple myeloma, leukemia, lung cancer, ovarian cancer, uterine cancer, cervical cancer, prostate cancer, liver cancer, colon cancer, pancreatic cancer, and brain cancer. Pre-cancerous and non-cancerous conditions characterized by excessive cell proliferation, and expression of a

CYP1B1, can be treated using the methods of the invention as well. For example, all carcinomas *in situ*, e.g., ductal carcinoma *in situ*, lobular carcinoma *in situ*, and cervical carcinoma *in situ*, as well as adenoma and benign polyps can be treated using the methods of the invention.

5 Patients that can be treated using the methods of the invention include those whose conditions are at early, intermediate, or advanced stages of development. Patients can receive treatment according to the invention before, during, or after other types of treatment, such as chemotherapy, radiation, or surgery, or can receive the treatment of the invention in the absence of any other 10 type of treatment. The methods of the invention can also be used as general prophylactic measures; to prevent conditions from arising in patients that are at risk, or have early signs, of developing a condition associated with excessive cellular proliferation, such as cancer; or to prevent recurrence of such a condition. Additional persons that can be treated, in particular, using vaccination methods of 15 the invention (see below), are those who are to donate cells, such as cytotoxic T lymphocytes, for use in the treatment of another (see below).

Central to the prophylactic and therapeutic methods of the invention is the pathway of cell-mediated immunity involving cytotoxic T lymphocytes (CTLs). In this pathway, an antigen is taken up and processed by an antigen 20 presenting cell, so that a peptide of the antigen is presented on the surface of the cell, in the context of MHC. Such antigen presenting cells then activate cytotoxic T lymphocytes, in an MHC-restricted fashion, to proliferate and kill target cells that express the antigen.

25 The prophylactic and therapeutic methods of the invention intervene in this pathway at different levels. For example, in one of these methods, a CYP1B1 antigen is administered to a patient, in whom the antigen is taken up by antigen presenting cells, which in turn activate CTLs. In another of these methods, an antigen presenting cell is contacted with a CYP1B1 antigen *ex vivo*, where it takes up, processes, and presents the antigen, in the context of MHC. Such *ex vivo* 30 stimulated APCs are then administered to a patient, in whom they specifically activate CTLs. In yet another of these methods, CTLs are activated *ex vivo* with

APCs presenting CYP1B1 peptides, and the activated CTLs are then administered to a patient. These methods, each of which includes numerous variations, are described in further detail below. Also, it is noted that all of these methods can be carried out with CYP1B1 peptides alone or, preferably, in combination with 5 another (or more) tumor associated antigen polypeptides or peptides (e.g., telomerase).

As is noted above, the prophylactic and therapeutic methods of the invention include one in which CYP1B1, or a fragment thereof that binds to MHC, is administered to a patient, in whom the antigen or fragment is taken up 10 by and processed within an antigen presenting cell, which in turn activates a cytotoxic T cell in the patient. This vaccination method can be carried out using CYP1B1, one or more MHC-binding peptides of CYP1B1, and, in addition to these (or a combination thereof), one or more universal TAAs or one or more MHC-binding peptides of more than one universal TAA, or a combination 15 thereof. Optionally, the antigen can be administered in combination with an adjuvant to enhance the anti-TAA immune response, or the antigen can be packaged into a delivery system (see below).

Any reagent including CYP1B1 or a MHC-binding peptide thereof can be used for vaccination. These include, without limitation, full length CYP1B1, 20 MHC-binding fragments of CYP1B1, as well as fusion proteins including CYP1B1 and MHC-binding fragments thereof. Peptides or polypeptides including CYP1B1 peptides and polypeptides can include 8, 9, 10, 11, 12, or more amino acid stretches having sequence identity with a region of CYP1B1. For example, the peptides can include nine amino acid stretches, in which seven, 25 eight, or all nine of the amino acids in the CYP1B1 peptide nine amino acid sequence are identical to a region of nine amino acids in CYP1B1. In addition, a CYP1B1 peptide or polypeptide can include up to 533 amino acids that are identical to an amino acid sequence found in CYP1B1, for example, 9-20, 20-40, 40-80, 80-200, or 200-533 amino acids that are identical to an amino acid 30 sequence found in CYP1B1. Polypeptides containing CYP1B1 peptides can

contain additional amino acid stretches that do not correspond to the amino acid sequence of CYP1B1.

To vaccinate a patient to elicit a CYP1B1-specific immune response in the patient, it is necessary to obtain large amounts of a CYP1B1 protein or peptide, and this can be accomplished by numerous standard methods, for example, chemical synthesis (e.g., Fmoc methods (Sigma Genosys); see above) or expression in eukaryotic or prokaryotic cells.

Recombinant CYP1B1 peptides can be overexpressed *in vivo* by introducing coding sequences of the peptides into various types of cells, or *in vitro*, using cell-free expression systems that are known in the art. The peptide products can then be purified for generating CYP1B1-specific CTLs *ex vivo* and for vaccine production. Purified CYP1B1 peptides are also useful for diagnostic assays that measure the presence of CYP1B1-specific CTLs in a test sample. For example, the presence (or increased levels) of CYP1B1-specific CTLs in a sample from a subject who has received an anti-CYP1B1 vaccination, relative to the level of CYP1B1-specific CTLs in a reference sample (such as a pre-vaccination sample from the patient), indicates that the patient has mounted a CYP1B1-specific immune response.

CYP1B1 peptides can be produced by chemical synthesis (e.g., by the methods described in *Solid Phase Peptide Synthesis*, 2nd ed., 1984, The Pierce Chemical Co., Rockford, IL, or by other methods known to those skilled in the art of peptide synthesis).

A wide variety of expression systems can be used to produce recombinant CYP1B1 peptides, polypeptides, fragments, fusion proteins, and amino acid sequence variants. CYP1B1 peptides can be produced in prokaryotic hosts (e.g., *E. coli*) or in eukaryotic hosts (e.g., *S. cerevisiae*, insect cells, such as Sf9 cells, or mammalian cells, such as COS-1, NIH 3T3, or HeLa cells). These cells are commercially available from, for example, the American Type Culture Collection, Rockville, Maryland (also see, e.g., Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, NY, 1998). The method of transformation and the choice of expression vehicle (e.g., expression vector)

depends on the host system selected. Transformation and transfection methods are described, *e.g.*, by Ausubel *et al.*, *supra*, and expression vehicles can be chosen from the numerous examples that are known in this field.

First, a nucleic acid molecule encoding a CYP1B1 peptide is introduced
5 into a plasmid or other vector, which is then used to transform living cells. Constructs in which a cDNA containing the entire CYP1B1 coding sequence, a fragment of the CYP1B1 coding sequence, amino acid variations of the CYP1B1 coding sequence, or fusion proteins of the aforementioned, inserted in the correct orientation into an expression plasmid, can be used for protein expression.
10 Prokaryotic and eukaryotic expression systems allow various immunogenic domains of CYP1B1 peptides or polypeptides to be recovered as fusion proteins, and then used for the generation of CYP1B1-specific CTLs. In some cases, for example, when a CYP1B1 peptide is to be expressed directly within a patient's cells, it may be desirable to express the CYP1B1 peptide under the control of an
15 inducible or tissue-specific promoter.

Typical expression vectors contain promoters that direct the synthesis of large amounts of mRNA corresponding to the inserted CYP1B1 peptide-encoding nucleic acid molecule in the plasmid-bearing cells. They can also include eukaryotic or prokaryotic "origin of replication" sequences, which allow for their
20 autonomous replication within the host organism, sequences that encode genetic traits that allow vector-containing cells to be selected in the presence of otherwise toxic drugs (such as antibiotics), and sequences that increase the efficiency with which the synthesized mRNA is translated. Stable, long-term vectors can be maintained as freely replicating entities within cells by using regulatory elements
25 of, for example, viruses (*e.g.*, the OriP sequences from the Epstein Barr Virus genome). Cell lines can also be produced that have the vector integrated into genomic DNA, and, in this manner, the gene product is produced on a continuous basis.

Expression of foreign sequences in bacteria such as *Escherichia coli*
30 requires insertion of a nucleic acid molecule encoding a polypeptide into a bacterial expression vector. Plasmid vectors in this category contain several

elements required for propagation of the plasmid in bacteria and expression of inserted DNA of the plasmid by the plasmid-carrying bacteria. Propagation of only plasmid-bearing bacteria is achieved by introducing into the plasmid 5 selectable marker-encoding sequences that allow plasmid-bearing bacteria to grow in the presence of otherwise toxic drugs (e.g., antibiotics). The plasmid also includes a transcriptional promoter that capable of producing large amounts of mRNA from the cloned gene. Such promoters may or may not be inducible promoters. The plasmid also, preferably, contains a polylinker to simplify insertion of the gene in the correct orientation within the vector. For example, in 10 a simple *E. coli* expression vector utilizing the lac promoter, the expression vector plasmid contains a fragment of the *E. coli* chromosome containing the lac promoter and the neighboring *lacZ* gene. In the presence of the lactose analog IPTG, RNA polymerase normally transcribes the *lacZ* gene, producing *lacZ* mRNA, which is translated into the encoded protein, β -galactosidase. The *lacZ* 15 gene can be cut out of the expression vector with restriction endonucleases and replaced by a CYP1B1 peptide gene sequence, or a fragment, fusion, or mutant thereof. When the resulting plasmid is transfected into *E. coli*, addition of IPTG and subsequent transcription from the lac promoter produces mRNA encoding the CYP1B1 polypeptide of interest, which is then translated into a polypeptide.

20 Once the appropriate expression vector containing a CYP1B1 gene is constructed, it is introduced into an appropriate host cell by transformation, transfection, or transduction techniques that are known in the art, including calcium chloride transformation, calcium phosphate transfection, DEAE-dextran transfection, electroporation, microinjection, protoplast fusion, and liposome-mediated transfection. The host cells that are transformed with the vectors of this 25 invention can include (but are not limited to) *E. coli* or other bacteria, yeast, fungi, insect cells (using, for example, baculoviral vectors for expression), human, mouse, or other animal cells. Mammalian cells can also be used to express CYP1B1 peptides using a vaccinia virus expression system, as is described by 30 Ausubel *et al.*, *supra*.

In vitro expression of CYP1B1 peptides, proteins, fusions, polypeptide fragments, or mutated versions thereof encoded by cloned DNA is also possible using the T7 late promoter expression system. Plasmid vectors containing late promoters and the corresponding RNA polymerases from related bacteriophages such as T3, T5, and SP6 can also be used for *in vitro* production of proteins from cloned DNA. *E. coli* can also be used for expression using an M13 phage such as mGPI-2. Furthermore, vectors that contain phage lambda regulatory sequences, or vectors that direct the expression of fusion proteins, for example, a maltose-binding protein fusion protein or a glutathione-S-transferase fusion protein, also can be used for expression in *E. coli*.

Eukaryotic expression systems permit appropriate post-translational modifications to expressed proteins. Transient transfection of a eukaryotic expression plasmid allows the transient production of CYP1B1 peptides by a transfected host cell. CYP1B1 peptides can also be produced by a stably-transfected mammalian cell line. A number of vectors suitable for stable transfection of mammalian cells are available to the public (e.g., see Pouwels *et al.*, *Cloning Vectors: A Laboratory Manual*, 1985, Supp. 1987), as are methods for constructing such cell lines (see, e.g., Ausubel *et al.*, *supra*). In one example, cDNA encoding a CYP1B1 peptide, protein, fragment, mutant, or fusion protein is cloned into an expression vector that includes the dihydrofolate reductase (DHFR) gene. Integration of the plasmid and, therefore, integration of the CYP1B1 peptide-encoding gene into the host cell chromosome is selected by inclusion of 0.01-300 μ M methotrexate in the cell culture medium (as is described by Ausubel *et al.*, *supra*). This dominant selection can be accomplished in most cell types. Recombinant protein expression can be increased by DHFR-mediated amplification of the transfected gene. Methods for selecting cell lines bearing gene amplifications are described by Ausubel *et al.*, *supra*. These methods generally involve extended culture in medium containing gradually increasing levels of methotrexate. The most commonly used DHFR-containing expression vectors are pCVSEII-DHFR and pAdD26SV(A) (described by Ausubel *et al.*, *supra*). The host cells described above or, preferably, a DHFR-deficient CHO

cell line (e.g., CHO DHFR- cells, ATCC Accession No. CRL 9096) are among those most preferred for DHFR selection of a stably-transfected cell line or DHFR-mediated gene amplification. Other drug markers can be analogously used.

5 Expression of proteins, such as those containing CYP1B1 peptides, in eukaryotic cells allows the production of large amounts of normal or mutant proteins for isolation and purification, and the use of cells expressing a CYP1B1 peptide-containing protein provides a functional assay system for antibodies generated against a CYP1B1 peptide of interest.

10 Another preferred eukaryotic expression system is the baculovirus system using, for example, the vector pBacPAK9, which is available from Clontech (Palo Alto, CA). If desired, this system can be used in conjunction with other protein expression techniques, for example, the myc tag approach described by Evan *et al.* (Mol. Cell Biol. 5:3610-3616, 1985).

15 Once a recombinant CYP1B1 protein is expressed, it can be isolated from the expressing cells by cell lysis followed by protein purification techniques, such as affinity chromatography. In this example, an anti-CYP1B1 peptide antibody, which can be produced by methods that are well-known in the art, can be attached to a column and used to isolate recombinant CYP1B1 peptide-containing proteins.

20 Lysis and fractionation of CYP1B1 peptide-harboring cells prior to affinity chromatography can be performed by standard methods (see, e.g., Ausubel *et al.*, *supra*). Once isolated, the recombinant protein can, if desired, be purified further, e.g., by high performance liquid chromatography (HPLC; e.g., see Fisher, *Laboratory Techniques in Biochemistry and Molecular Biology*, Work and

25 Burdon, Eds., Elsevier, 1980).

30 Preferably, CYP1B1 or a MHC-binding peptide thereof is administered to a patient in association with an adjuvant. For example, a chemical antigen (e.g., Freund's incomplete adjuvant; cytoxin; an aluminum compound, such as aluminum hydroxide, aluminum phosphate, or aluminum hydroxyphosphate; liposomes; ISCOMS; microspheres; protein chochleates; vesicles consisting of nonionic surfactants; cationic amphiphilic dispersions in water; oil/water

emulsions; muramidylidipeptide (MDP) and its derivatives such as glucosyl muramidylidipeptide (GMDP), threonyl-MDP, murametide and murapalmitin; and QuilA and its subfractions; as well as various other compounds such as monophosphoryl-lipid A (MPLA); gamma-inulin; calcitriol; and loxoribine) can 5 be used.

A biological response modifier, which is a soluble mediator that affects induction of an immune response, can also be used as an adjuvant. For example, cytokines (e.g., IL-2 and GM-CSF), chemokines, co-stimulatory molecules (e.g., B7, ICAM, class I monoclonal antibodies, stem cell factor, and stimulated T cells) 10 can be used. Also, bacterial products, such as toxins or, preferably, subunits or fragments thereof that have reduced (if any) toxicity, but maintained adjuvant activity.

Additional types of adjuvant molecules that can be used in the invention include, for example, biological modifiers of the death response (e.g., apoptosis 15 sensitizers) and compounds or treatment that increases the susceptibility of the target cell to treatment, such as radiation and chemotherapy. Also, increasing expression of CYP1B1 in the cell can increase susceptibility of the cell to treatment according to the invention.

Finally, as is described above, cellular adjuvants can be used in the 20 immunization methods of the invention. For example, a CYP1B1 peptide can be administered to a patient on the surface of an antigen presenting cell, in the context of MHC. In addition to professional antigen presenting cells, e.g., dendritic cells, CD40-activated B cells, irradiated tumor cells (e.g., in association 25 with GM-CSF), alternative antigen presenting cells, synthetic antigen presenting cells (e.g., lipid mycels and artificial APC-like scaffolds), and fusions of any of the above-listed cells can be used.

As an alternative to vaccination with a CYP1B1 protein or peptide, vaccination with a nucleic acid molecule that encodes such a protein or peptide can be used for vaccination. Such nucleic acid molecules can be administered as 30 "naked" DNA molecules, present in a plasmid or viral vector, or packaged into a liposome or cell, such as eukaryotic cell, prior to administration. The nucleic acid

molecules can be administered to a patient *in vivo*, or can be used to treat a cell *ex vivo* (e.g., an antigen presenting cell, such as a dendritic cell or a CD40-activated B cell), which is then administered to the patient. Alternatively, RNA, e.g., mRNA, can be used in these methods (see, e.g., Boczkowski *et al.*, *J. Exp. Med.* 5 184:465-472, 1996; *J. Exp. Med.* 186:1177-1182, 1997).

For *in vivo* expression, a gene that encodes a polypeptide that includes CYP1B1 or an MHC-binding peptide thereof must be delivered to cells in a form that can be taken up by the cells, in which a sufficient level of protein is expressed to induce an effective immune response. Retroviral, adenoviral, lentiviral, 10 poxviral, and other viral vectors are suited as nucleic acid expression vectors for *in vivo* delivery, because they show efficient infection and/or integration and expression; see, e.g., Cayouette *et al.*, *Hum. Gene Therapy*, 8:423-430, 1997; Kido *et al.*, *Curr. Eye Res.* 15:833-844, 1996; Bloomer *et al.*, *J. Virol.* 71:6641- 6649, 1997; Naldini *et al.*, *Science* 272:263-267, 1996; Miyoshi *et al.*, *Proc. Nat. 15 Acad. Sci., U.S.A.*, 94:10319-1032, 1997; *Vaccines: New Approaches to Immunological Problems*, R. W. Ellis (Ed.), Butterworth-Heinemann, Boston. For example, any DNA fragment that encodes a polypeptide that contains a CYP1B1 peptide can be cloned into a retroviral vector and transcribed *via* its endogenous promoter, *via* an exogenous promoter, *via* a promoter specific for the target cell 20 type of interest, or, in the case of retroviral vectors, *via* the retroviral long terminal repeat. Other viral vectors that can be used include adenovirus, adeno-associated virus, poxviruses, such as vaccinia virus or bovine papilloma virus, or a herpes virus, such as Epstein-Barr Virus.

Gene transfer *in vivo* can also be achieved by non-viral means. For 25 example, a plasmid vector that encodes a polypeptide that contains a CYP1B1 peptide can be injected directly into skeletal muscle or cardiac muscle by previously described methods (e.g., Wolff *et al.*, *Science*, 247:1465-1468, 1990). Expression vectors injected into skeletal muscle *in situ* are taken up into muscle cell nuclei and used as templates for expression of their encoded proteins. 30 CYP1B1 peptide-encoding genes that are engineered to contain a signal peptide are secreted from CYP1B1 peptide-expressing muscle cells, after which they

induce an immune response. Gene transfer into cells within the tissues of a living animal also can be achieved by lipofection (Felgner *et al.*, Proc. Natl. Acad. Sci. USA 84:7413, 1987; Ono *et al.*, Neurosci. Lett. 117:259, 1990; Brigham *et al.*, Am. J. Med. Sci. 298:278, 1989; Staubinger *et al.*, Meth. Enz. 101:512, 1983), or 5 asialoorosomucoid-polylysine conjugation (Wu *et al.*, J. Biol. Chem. 263:14621, 1988; Wu *et al.*, J. Biol. Chem. 264:16985, 1989), and analogous methods.

Retroviral vectors, adenoviral vectors, adenovirus-associated viral vectors, or other viral vectors also can be used to deliver genes encoding CYP1B1 peptides or polypeptides to cells *ex vivo*. Numerous vectors useful for this 10 purpose are generally known (see, *e.g.*, Miller, Human Gene Therapy 15-14, 1990; Friedman, Science 244:1275-1281, 1989; Eglitis *et al.*, BioTechniques 6:608-614, 1988; Tolstoshev *et al.*, Curr. Opin. Biotech. 1:55-61, 1990; Sharp, The Lancet 337:1277-1278, 1991; Cornetta *et al.*, Nucl. Acid Res. and Mol. Biol. 36:311-322, 1987; Anderson, Science 226: 401-409, 1984; Moen, Blood Cells 15 17:407-416, 1991; Miller *et al.*, Biotech. 7:980-990, 1989; Le Gal La Salle *et al.*, Science 259:988-990, 1993; and Johnson, Chest 107:77S-83S, 1995). Retroviral vectors are particularly well developed and have been used in clinical settings (Rosenberg *et al.*, N. Engl. J. Med 323:370, 1990; Anderson *et al.*, U.S. Patent 20 No. 5,399,346).

Gene transfer into cells *ex vivo* can also be achieved by delivery of non-viral vectors, such as expression plasmids, using methods such as calcium phosphate or DEAE dextran transfection, electroporation, and protoplast fusion. Liposomes can also be potentially beneficial for delivery of DNA into a cell.

Cells that are to be transduced or transfected *ex vivo* can be obtained from 25 a patient (*e.g.*, peripheral blood cells, such as B cells or dendritic cells, bone marrow stem cells, or cells from a tumor biopsy) prior to transfection, and re-introduced after transfection. However, the cells also can be derived from a source other than the patient undergoing gene transfer.

In the constructs described above, CYP1B1 peptide expression can be 30 directed from any suitable promoter (*e.g.*, the human cytomegalovirus (CMV), simian virus 40 (SV40), or metallothionein promoters), and regulated by any

appropriate mammalian regulatory element. For example, if desired, enhancers known to preferentially direct gene expression in skeletal muscle cells can be used to direct CYP1B1 peptide expression for vaccination *in situ*. The enhancers used can include, without limitation, those that are characterized as tissue- or cell-specific in their expression.

Conventional pharmaceutical practice can be employed to provide suitable formulations or compositions to administer CYP1B1 peptide or nucleic acid vaccinations for treatment of, or prophylaxis against, cancer. CYP1B1 peptides, CYP1B1 polypeptides, and CYP1B1 nucleic acid molecules can be administered within a pharmaceutically-acceptable diluent, carrier, or excipient, in unit dosage form. Administration can begin before a patient is symptomatic. Any appropriate route of administration can be employed, for example, administration can be parenteral, intravenous, intra-arterial, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, by suppositories, or oral administration. Therapeutic formulations can be in the form of liquid solutions or suspensions; for oral administration, formulations can be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols. An adjuvant, *e.g.*, as listed above, can be included with the formulation.

Methods well known in the art for making formulations are found, for example, in *Remington's Pharmaceutical Sciences*, (18th edition), ed. A. Gennaro, 1990, Mack Publishing Company, Easton, PA. Formulations for parenteral administration can, for example, contain excipients, sterile water, or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers can be used to control the release of the compounds. Other potentially useful parenteral delivery systems for CYP1B1 peptides, polypeptides, and CYP1B1 nucleic acid molecules include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation can contain excipients, for example, lactose, or can be aqueous

solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or can be oily solutions for administration in the form of nasal drops, or as a gel.

As is mentioned above, in addition to the vaccination methods described

5 above, which result in the activation of antigen-specific, MHC-restricted CTLs *in vivo*, such cells (*i.e.*, antigen-specific, MHC-restricted CTLs) can be generated *in vitro*, and then administered to patients. Any cell that expresses an endogenous or exogenously-introduced major histocompatibility antigen-encoding gene can be used to present a CYP1B1 peptide to generate CYP1B1- specific CTLs *in vitro*.

10 In one variation of this approach, a peptide-presenting cell expresses an endogenously or exogenously-introduced CYP1B1 polypeptide-encoding gene. Expression of endogenous CYP1B1 in antigen-presenting cells can be stimulated as described in Schultze *et al.*, *supra*, by cytokines, such as IL-2, or by other molecules that are known to those of skill in this art to stimulate CYP1B1

15 expression.

In another variation, the antigen presenting cells are pulsed with CYP1B1 or MHC-binding peptide thereof, and the pulsed cells are then used to generate CTLs for administration to a patient. Preferably, the CTLs used in these methods are obtained from the patient to whom they are to ultimately be administered (*i.e.*, the cells are autologous). Alternatively, donor cells (*i.e.*, allogeneic cells) can be used in this method.

Finally, methods in which any of the above-described immunotherapeutic approaches are combined are included in the invention. For example, a patient may be treated with an *ex vivo*, CYP1B1-activated CTL and/or an *ex vivo*,
20 CYP1B1-pulsed APC (*e.g.*, a DC or a CD40-activated B cell), and this treatment can be carried out before, during, or after a vaccination approach (see above). In addition to combining the approaches, each approach (or a combination thereof) can employ multiple peptides of CYP1B1, peptides of other TAAs, or a combination thereof.

Measurement of CYP1B1-specific CTL levels in patients, CTL donors, and CYP1B1-specific CTL preparations generated ex vivo

Patients who have one or more tumors containing CYP1B1-expressing tumor cells and patients who are at risk for developing such tumors can be 5 vaccinated with compositions containing one or more CYP1B1 peptides, CYP1B1 polypeptides, CYP1B1 nucleic acid molecules, cells presenting a CYP1B1 peptide, or mixtures thereof (other TAA (e.g., hTERT) polypeptides, peptides, nucleic acid molecules, or APCs can also be included). Subjects to be used as 10 donors of CYP1B1-specific CTLs for transfer into patients can be similarly vaccinated. Levels of CYP1B1-specific CTLs that result from CYP1B1-specific vaccination of patients or other subjects, or *ex vivo* generation of CYP1B1 specific CTLs, can be monitored using well-known methods. An increase in the 15 level of CYP1B1-specific CTLs in a test sample from a vaccinated subject or a CTL culture stimulated with CYP1B1 *ex vivo*, relative to a reference sample (e.g., a pre-vaccination or pre-stimulation sample), indicates that a CYP1B1-specific CTL response has been stimulated in a vaccinated subject or CYP1B1-stimulated 20 CTL culture. Preferably the increase is by at least 50%, more preferably, at least 100%, still more preferably, at least 200%, and most preferably, at least 400%. In addition, the efficacy of non-antigen-specific immunotherapies (e.g., administration of IL-2 or interferon) against tumors containing CYP1B1-expressing cells can be monitored using similar approaches.

Levels of CYP1B1-specific CTLs can also be assessed in naive subjects who have not received CYP1B1 vaccinations or other treatment for the purpose of 25 generating CYP1B1-specific CTLs. Since some types of tumors (e.g., malignant melanoma, renal cell carcinoma, and non-Hodgkin's lymphoma) themselves elicit immune responses in their hosts, an increase in the level of CYP1B1-specific CTLs cells in a patient sample, compared to the level in a reference sample from a normal subject who does not have a tumor, or in a reference sample that was 30 previously obtained from the patient, can indicate the development of a tumor in a patient not known to have a tumor or an increase in tumor burden (e.g., increased

tumor size, or the development or increase in metastatic tumors) in a patient known to have a tumor.

One approach by which the level of CYP1B1-specific CTLs can be measured is using standard cytotoxicity assays, such as the Cr⁵¹ release assay 5 (Schultze *et al.*, *J. Clin. Invest.* 100:2757, 1997), which is described above. Another approach for measuring the level of CYP1B1-specific CTLs involves measuring the binding of peptide-specific CTLs to a tetrameric peptide/MHC complex *in vitro*, as is described by Altman *et al.* (*Science* 274:94-96, 1996). Briefly, a fusion protein containing an HLA heavy chain molecule, such as 10 HLA-A*0201, plus a peptide that is a substrate for biotinylation at the C-terminus of the HLA polypeptide, is produced. The fusion protein is folded *in vitro* in the presence 2-microglobulin and a CYP1B1 peptide ligand. The purified MHC/CYP1B1 peptide complexes are then biotinylated at the C-terminus of the HLA heavy chain, and tetramers are produced by mixing the biotinylated 15 MHC/CYP1B1 peptide complexes with phycoerythrin-labeled deglycosylated avidin at a molar ratio of 4:1. Samples that contain CTLs (such as blood samples or *ex vivo* cultures) are mixed with the CYP1B1 peptide/MHC tetrameric complexes and the relative amount of CYP1B1-specific CTLs that bind to the CYP1B1 peptide/MHC tetrameric complexes can be measured for each sample by 20 flow cytometry, using methods described by Altman *et al.*, *supra*, and by other methods known to those of skill in this art. Another method that can be used is ELISPOT (Herr *et al.*, *J. Immunol. Methods* 203:141-152, 1997).

Other Embodiments

25 All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication or patent application was specifically and individually indicated to be incorporated by reference.

30 While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications, and this application is intended to cover any variations, uses, or

adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure come within known or customary practice within the art to which the invention pertains and can be applied to the essential features hereinbefore set forth, and follows in the scope of
5 the appended claims.

What is claimed is:

APPENDIX A

Search Report

HLA-A*0201 Nonamers

HLA-A*0201 Decamers

HLA-A*0201 Octamers

HLA-A*0202 Nonamers

HLA-A*0202 Decamers

HLA-A*0203 Nonamers

HLA-A*0203 Decamers

HLA-A*0203 Octamers

HLA-A1 Nonamers

HLA-A1 Decamers

HLA-A26 Nonamers

HLA-A26 Decamers

HLA-B*0702 Nonamers

HLA-B*0702 Decamers

HLA-B*1510 Nonamers

HLA-B*2705 Nonamers

HLA-B8 Octamers

HLA-B8 Nonamers

HLA-A*0201 Nonamers

Pos 1 2 3 4 5 6 7 8 9
 25 L L L S V L A T V
 22 T L L L L L S V L
 528 L L D S A V Q N L
 479 Q L F L F I S I L
 190 F L D P R P L T V
 377 N L P Y V L A F L
 344 L L F T R Y P D V
 334 T L S T A L Q W L
 239 S L V D V M P W L
 58 P L I G N A A A V
 24 L L L L S V L A T
 21 T T L L L L L S V
 170 V L S E A R E L V
 17 S I Q Q T T L L L
 521 T L R E S M E L L
 510 T I K P K S F K V
 196 L T V V A V A N V
 76 R L A R R Y G D V

HLA-A1 Nonamers

Pos 1 2 3 4 5 6 7 8 9
 372 M G D Q P N L P Y
 241 V D V M P W L Q Y
 404 T A N T S V L G Y
 190 F L D P R P L T V
 185 S A D G A F L D P
 174 A R E L V A L L V
 171 L S E A R E L V A
 165 V L E G H V L S E
 7 P N D P W P L N P
 445 F L D K D G L I N
 341 W L L L L F T R Y
 522 L R E S M E L L D
 336 S T A L Q W L L L
 218 D P E F R E L L S
 206 S A V C F G C R Y
 129 G R S M A F G H Y
 439 N F D P A R F L D
 378 L P Y V L A F L Y

HLA-B*0702 Nonamers

Pos 1 2 3 4 5 6 7 8 9
 192 D P R P L T V V A
 51 P P G P F A W P L
 414 I P K D T V V F V
 375 Q P N L P Y V L A
 288 A P R D M M D A F
 399 I P H A T T A N T
 250 F P N P V R T V F
 194 R P L T V V A V A
 512 K P K S F K V N V
 50 A P P G P F A W P
 320 V P A T I T D I F
 117 R P A F A S F R V
 89 L G S C P I V V L
 57 W P L I G N A A A
 474 E L S K M Q L F L
 395 V P V T I P H A T
 183 R G S A D G A F L
 309 H G G G A R L D L

HLA-B*2705 Nonamers

Pos 1 2 3 4 5 6 7 8 9
 232 G R T V G A G S L
 37 Q R L L R Q R R R
 443 A R F L D K D G L
 258 F R E F E Q L N R
 145 R R A A H S M M R
 79 R R Y G D V F Q I
 347 T R Y P D V Q T R
 467 K R R C I G E E L
 265 N R N F S N F I L
 116 D R P A F A S F R
 514 K S F K V N V T L
 469 R C I G E E L S K
 182 V R G S A D G A F
 129 G R S M A F G H Y
 47 L R S A P P G P F
 40 L R Q R R R Q L R
 175 R E L V A L L V R
 144 Q R R A A H S M M

39 LLRQRRRQL	324 ITDIFGASQ	14 NPLSIQQT	479 QLFLFISIL
525 SMELLDASV	258 FREFEQLNR	438 ENFDPARFL	472 GEELSKMQL
337 TALQWLLLL	216 HDDPEFREL	402 ATTANTSVL	383 AFLYEAMRF
246 WLQYFPNPV	73 SFARLARRY	173 EARELVALL	295 AFILSAEKK
235 VGAGSLVDV	499 EPAKMNFSY	64 AAVGQAAHL	289 PRDMMDAFI
172 SEARELVAL	292 MMDFILSA	48 RSAPPGPFA	163 RQVLEGHVL
23 LLLLLSVLA	137 YSEHWKVQR	514 KSFKVNVTL	43 RRRQLRSAP
470 CIGEELSKM	81 YGDVFQIRL	467 KRRCIGEEL	509 LTIKPKSFK
380 YVLAFLYEA	349 YPDVQTRVQ	370 PCMGDQPNL	370 PCMGDQPNL
316 DLENVPATI	497 PNEPAKMNF	307 DSHGGGARL	307 DSHGGGARL
292 MMDFILSA	428 NHDPLKWPN	172 SEARELVAL	294 DAFLSAEK
173 EARELVALL	415 PKDTVVFVN	159 QPRSRQVLE	213 RYSHDDPEF
88 RLGSCPPIV	359 ELDQVVGRD	99 GERAIHQAL	188 GAFLDPRPL
64 AAVGQAAHL	228 NEEFGRTVG	69 AAHLSFARL	153 RNFFTRQPR
520 VTLRESMEL	20 QTLLLLLS	8 NDPWPLNPL	87 IRLGSCPPIV
336 STALQWLLL	530 DSAVQNLQA	6 SPNDPWPLN	72 LSFARLARR
312 GARLDLENV	447 DKDGLINKD	501 AKMNFSYGL	44 RRQLRSAPP
249 YFPNPVRTV	316 DLENVPATI	499 EPAKMNFSY	36 GQRLLRQRR
200 AVANVMSAV	215 SHDDPEFRE	496 NPNEPAKMN	22 TLLLLLSSL
165 VLEGHVLSE	33 VHVGQRLR	424 QWSVNHDPL	520 VTLRESMEL
89 LGSCPPIVVL	528 LLDASVQNL	349 YPDVQTRVQ	494 RANPNEPAK
15 PLSIQQTTL	525 SMELLDASV	346 FTRYPDVQT	481 FLFISILAH
481 FLFISILAH	505 FSYGLTIKP	336 STALQWLLL	468 RRCIGEELS
474 ELSKMQLFL	456 LTSRVMIFS	331 SQDTLSTAL	461 MIFSVGKRR
419 VVFVNQWSV	393 SFVPVTIPH	327 IFGASQDTL	460 VMIFSVGKR
414 IPKDTVVFV	376 PNLPYVLA	284 RPGAAPRDM	459 RVMIFSVGK
381 VLAFLYEA	333 DTLSTALQW	216 HDDPEFREL	451 LINKDLTSR
373 GDQPNLPYV	331 SQDTLSTAL	189 AFLDPRPLT	446 LDKDGLINK
355 RVQAELDQV	314 RLDLENVPA	163 RQVLEGHVL	341 WLLLLFTRY
338 ALQWLLLLF	305 AGDSHGGGA	158 RQPRSRQVL	340 QWLLLLFTR
282 SLRPGAAPR	299 SAEKKAAGD	115 ADRPAFASF	337 TALQWLLL
169 HVLSAREL	240 LVDVMPWLQ	53 GFAWPLIG	313 ARLDLENVP
95 VVLNGERAI	114 FADRPFAFAS	47 LRSAPPGPF	283 LRPGAAPRD
86 QIRLGSCPI	21 TTLLLLLSV	39 LLRQRRRQL	260 EFEQLNRNF
69 AAHLSFARL	476 SKMQLFLFI	31 ATVHVGQRL	247 LQYFPNPVR
451 LINKDLTSR	471 IGEELSKMQ	18 IQQTTLLL	161 RSRQVLEGH
450 GLINKDLTS	453 NKDLTSRVM	17 SIQQTTLLL	158 RQPRSRQVL
412 YHIPKDTVV	397 VTIPHATTA	15 PLSIQQTTL	124 RVVSGGRSM
409 VLGYHIPKD	385 LYEA MRFSS	11 WPLNPLSIQ	89 LGSCPPIVVL
402 ATTANTSVL	365 GRDRLPCMG	528 LLDASVQNL	69 AAHLSFARL
342 LLLLFTTRYP	357 QAEILDQVVG	521 TLRESMELL	64 AAVGQAAHL
322 ATITDIFGA	279 HCESLRPGA	448 KDGLINKDL	16 LSIQQTLL
272 ILDKFLRHC	272 ILDKFLRHC	443 ARFLDKDGL	508 GLTIKPKSF
191 LDPRPLTVV	260 EFEQLNRNF	436 NPENFDPAR	504 NFSYGLTIK
87 IRLGSCPPIV	227 HNEEFGRTV	430 DPLKWPNPE	497 PNEPAKMNF
55 FAWPLIGNA	221 FRELLSHNE	390 RFSSFVPT	474 ELSKMQLFL
18 IQQTTLLL	91 SCPIVVNL	377 NL PYVLAFL	448 KDGLINKDL
514 KSFKVNVTL	90 GSCPIVVNL	337 TALQWLLL	438 ENFDPARFL
501 AKMNFSYGL	490 QCDFRANPN	334 TLSTALQWL	408 SVLGYHIPK
460 VMIFSVGKR	472 GEELSKMQL	290 RDMMMDAFI	389 MRFSSFVPT
457 TSRVMIFSV	440 FDPARFLDK	229 EEFGRTVGA	382 LAFLYEAMR
356 VQAELDQVV	436 NPENFDPAR	218 DPEFRELLS	376 PNLPYVLA
319 NVPATITDI	426 SVNHDPLKW	148 AHSMMRNFF	361 DQVVGRDRL
315 LDLENVPAT	353 QTRVQAELD	19 QQTLLL	358 AELDQVVGR
314 RLDLENVPA	338 ALQWLLLLF	16 LSIQQTTL	352 VQTRVQAEEL
297 ILSAEKAA	289 PRDMMDAFI	9 DPWPLNPLS	327 IFGASQDTL
296 FILSAEKKA	271 ILDKFLRH	493 FRANPNEPA	306 GDSHGGGAR
233 RTVGAGSLV	233 RTVGAGSLV	476 SKMQLFLFI	290 RDMMMDAFI
188 GAFLDPRPL	98 NGERAIHQ	441 DPARFLDKD	282 SLRPGAAPR

180 LLVRGSADG	48 RSAPPGPFA	434 WPNPENFDP	277 LRHCESLRP
131 SMAFGHYSE	31 ATVHVGQRL	413 HIPKDTVVF	275 KFLRHCESL
102 AIHQALVQQ	17 SIQQTTLLL	376 PNLPYVLAFL	269 SNFILDKFL
96 VLNGERAH	516 FKVNVTLRE	374 DQPNLPYVL	256 TVFREFEQL
32 TVHVGQRLL	379 PYVLAFLYE	369 LPCMGDQPN	250 FPNPVRTVF
31 ATVHVGQRL	291 DMMDAFILS	361 DQVVGRDRL	221 FRELLSHNE
29 VLATVHVGQ	282 SLRPGAAAPR	352 VQTRVQAEAL	219 PEFRELLSH
27 LSVLATVHV	266 RNFNSNFIELD	335 LSTALQWLL	208 VCFGCRYSH
16 LSIQQTTLL	250 FPNPVRTVF	329 GASQDTLST	202 ANVMSAVCF
8 NDWPPLNPL	234 TVGAGSLVD	314 RLDLENVPA	183 RGSADGAF
452 INKDLTSRV	160 PRSRQVLEG	297 ILSAEKKAA	174 ARELVALLV
401 HATTANTS	156 FTRQPRSRQ	275 KFLRHCESL	169 HVLSEAREL
397 VTIPHATTA	101 RAIHQALVQ	269 SNFILDKFL	132 MAFGHYSEH
307 DSHGGGARL	12 PLNPLSIQQ	256 TVFREFEQL	106 ALVQQGSASF
275 KFLRHCESL	503 MNFSYGLTI	252 NPVRTVFR	81 YGDVFQIRL
256 TVFREFEQL	481 FLFISILAH	244 MPWLOYFPN	80 RYGDVFQIR
199 VAVANVMSA	475 LSKMQLFLF	239 SLVDVMPWL	78 ARRYYGDVFQ
179 ALLVRGSAD	408 SVLGYHIPK	235 VGAGSLVDV	31 ATVHVGQRL
79 RRYGDVFQI	403 TTANTSVLG	217 DDPEFRELL	15 PLSIQQTTL
19 QQTTLLELL	402 ATTANTSVL	191 LDPRPLTVV	531 SAVQNLQAK
4 SLSPNDPWP	392 SSFVPVTIP	188 GAFLDPRPL	506 SYGLTIKPK
486 IAHQCDFR	363 VVGRDRLPC	125 VVSGGRSMA	485 SILAHQCD
477 KMQLFLFIS	346 FTRYPDVQT	113 AFADRPFA	470 CIGEELSKM
443 ARFLDKDGL	337 TALQWLLL	81 YGDVFQIRL	458 SRVMIFSVG
411 GYHIPKDTV	318 ENVPATITD	22 TLLLLSVL	444 RFLDKDGLI
406 NTSVLGYHI	309 HGGGARLDL	5 LSPNDPWPL	421 FVNQWSVNH
394 FVPVTIPHA	307 DSHGGGARL	520 VTLRESMEL	413 HIPKDTVVF
384 FLYEAMRFS	184 GSADGAFLD	513 PKSFKVNT	365 GRDRLPCMG
352 VQTRVQAEAL	121 ASFRVVSGG	479 QLFLFISIL	354 TRVQAELDQ
343 LLLFTRYPD	115 ADRPAFASF	472 GEELSKMQL	338 ALQWLLLLF
331 SQDTLSTAL	71 HLSFARLAR	454 KDLTSLRVMI	335 LSTALQWLL
329 GASQDTLST	49 SAPPGPFAW	396 PTIPHATT	331 SQDTLSTAL
327 IFGASQDTL	24 LLLSVLAT	391 FSSFVPVTI	271 FILDKFLRH
326 DIFGASQDT	19 QQTTLLELL	389 MRFSSFVPV	270 NFIELDKFLR
271 FILDKFLRH	18 IQQTTLLELL	378 LPYVLAFLY	268 FSNFIELDK
236 GAGSLVDVM	16 LSIQQTTLL	338 ALQWLLLLF	267 NFSNFIELDK
232 GRTVGAGSL	520 VTLRESMEL	317 LENVPATIT	236 GAGSLVDVM
227 HNEEFGRTV	514 KSFKVNVT	305 AGDSHGGGA	223 ELLSHNEEF
216 HDDPEFREL	509 LTIKPKSF	292 MMDAFLSA	173 EARELVALL
193 PRPLTVVAV	478 MQLFLFISI	265 NRNFSNFI	138 SEHWKVQRR
177 LVALLVRGS	474 ELSKMQLFL	249 YFPNPVRTV	126 VSGGRSMAF
176 ELVALLVRG	469 RCIGEELSK	233 RTVGAGSLV	123 FRVVSGGRS
135 GHYSEHWKV	463 FSVGKRCI	232 GRTVGAGSL	115 ADRPAFASF
107 LVQQGSAFA	450 GLINKDLTS	213 RYSHDDPEF	112 SAFADRPFA
512 KPKSFKVNV	417 DTVVFVNQW	202 ANVMSAVCF	99 GERAIHQAL
503 MNFSYGLTI	412 YHIPKDTVV	200 AVANVMSAV	93 PIVVLNGER
502 KMNFSYGLT	406 NTSVLGYHI	193 PRPLTVVAV	75 ARLARRYGD
476 SKMQLFLFI	391 FSSFVPVTI	190 FLDPRPLTV	63 AAAVGQAAH
467 KRRCIGEEL	322 ATITDIFGA	181 LVRGSAADGA	33 VHVGQRL
454 KDLTSLRVMI	308 SHGGGARLD	174 ARELVALLV	32 TVHVGQRL
389 MRFSSFVPV	268 FSNFIELDK	171 LSEARELVA	528 LLDSAVQNL
387 EAMRFSSFV	205 MSAVCFGCR	169 HVLSEAREL	515 SFKVNVTLR
341 WLLLFLTRY	196 LTVVAVANV	126 VSGGRSMAF	501 AKMNF SYGL
339 LQWLLLLFT	175 RELVALLVR	112 SAFADRPFA	495 ANPNEPAKM
330 ASQDTLSTA	83 DVFQIRLGS	106 ALVQQGSASF	473 EELSKMQLF
309 HGGGARLDL	66 VGQAAHLSF	92 CPIVVLNGE	437 PENFDPARF
269 SNFILDKFL	9 DPWPLNPLS	87 IRLGSCPIV	432 LKWPNPENF
181 LVRGSAADGA	4 SLSPNDPWP	79 RRYGDVFQI	425 WSVNHDPLK
178 VALLVRGSA	523 RESMELLD	77 LARRYGDVF	402 ATTANTSVL

162 SRQVLEGHV	510 TIKPKSFKV	62 NAAAVGQAA	377 NLPYVLAFL
150 SMMRNFFTR	480 LFLFISILA	58 PLIGNAAAV	374 DQPNLPYVL
125 VVSGGRSMA	458 SRVMIFSVG	56 AWPLIGNAA	372 MGDQPNLPY
106 ALVQQGSAF	446 LDKDGLINK	32 TVHVGQRLL	367 DRLPCMGDQ
81 YGDVFQIRL	425 WSVNHDPLK	24 LLLLSQLAT	309 HGGGARLDL
63 AAAVGQAAH	407 TSVLGYHIP	530 DSAVQNLQA	263 QLNRRNFSNF
28 SVLATVHVG	354 TRVQAELDQ	503 MNFSYGLTI	239 SLVDVMPWL
26 LLSVLATVH	339 LQWLLLLFT	463 FSVGKRRCI	216 HDDPEFREL
527 ELLDSAVQN	335 LSTALQWLL	412 YHIPKDTVV	212 CRYSHDDPE
517 KVNVTLRES	329 GASQDTLST	411 GYHIPKDTV	197 TVVAVANVM
508 GLTIKPKSF	311 GGARLDLEN	406 NTSVLGYHI	193 PRPLTVVAV
485 SILAHQCDF	281 ESLRPGAAP	387 EAMRFSSFV	172 SEARELVAL
478 MQLFLFISI	277 LRHCESLRP	350 PDVQTRVQA	160 PRSRQVLEG
463 FSVGKRRCI	267 NFSNFIILDK	339 LQWLLLLFT	157 TRQPRSRRQV
455 DLTSRVMIF	255 RTVFREFEQ	315 LDLENVPAT	147 AAHSMMRNF
445 FLDKDGLIN	219 PEFRELLSH	289 PRDMMDAFI	137 YSEHWKVQR
444 RFLDKDGLI	214 YSHDDPEFR	280 CESLRPGAA	100 ERAIHQALV
413 HIPKDTVVF	161 RSRQVLEGH	264 LNRNFSNFI	51 PPGPFAWPL
391 FSSFVPTI	126 VSGGRSMAF	253 PVRTVFREF	39 LLRQRRLRQL
358 AELDQVVGR	125 VVSGGRSMA	248 QYFPNPVRT	35 VGQRLLRQR
335 LSTALQWLL	88 RLGSCPPIVV	170 VLSEARELV	26 LLSVLATVH
264 LNRNFSNFI	53 GPFAWPLIG	118 PAFASFRVV	19 QQTTLLLL
224 LLSHNEEFG	50 APPGPFAWP	100 ERAIHQALV	18 IQQTTLLLL
217 DDPEFRELL	41 RQRRRQLRS	88 RLGSCPPIVV	17 SIQTTLLL
194 RPLTVVAVA	34 HVGQRLLRQ	86 QIRLGSCPI	8 NDPWPLNPL
183 RGSADGAFL	10 PWPLNPLSI	67 GQAAHLSFA	521 TLRESMELL
174 ARELVALLV	3 TSLSPNDPW	66 VGQAAHLSF	499 EPAKMNFSY
166 LEGHVLSEA	2 GTSLSPNDP	61 GNAAAVGQA	493 FRANPNEPA
164 QVLEGHVLS	515 SFKVNVTLR	27 LSVLATVHV	455 DLTSRVMIF
157 TRQPRSRRQV	465 VGKRCIGE	524 ESMELLDSA	454 KDLTSRVM
124 RVVSGGRSM	434 WPNPENFDP	457 TSRVMIFSV	436 NPENFDPAR
120 FASFRVVSG	416 KDTVVVFVNQ	452 INKDLTSRV	393 SFVPVTIPH
118 PAFASFRVV	386 YEAMRFSSF	435 PNPENFDPA	386 YEAMRFSSF
105 QALVQQGSA	347 TRYDPDVQTR	397 VTIPHATTA	378 LPYVLAFLY
99 GERAIHQAL	330 ASQDTLSTA	386 YEAMRFSSF	336 STALQWLL
59 LIGNAAAVG	328 FGASQDTLS	383 AFLYEAMRF	284 RPGAAPRDM
46 QLRSAPPGP	286 GAAPRDMMD	373 GDQPNLPYV	259 REFEQLNRN
38 RLLRQRRRQ	253 PVRTVFREF	356 VQAELDQVV	253 PVRTVFREF
5 LSPNDPWPL	239 SLVDVMPWL	355 RVQAELDQV	242 DVMPWLQYF
535 NLQAKETCQ	238 GSLVDVMPW	348 RYDPDVQTRV	241 DVMPWLQY
532 AVQNLQAKE	226 SHNEEFGR	330 ASQDTLSTA	186 ADGAFLDPR
531 SAVQNLQAK	192 DPRPLTVVA	326 DIFGASQDT	167 EGHVLSEAR
524 ESMELLDSA	189 AFLDPRPLT	322 ATIDIFGA	148 AHSMMRNFF
483 FISILAHQC	170 VLSEARELV	319 NVPATITDI	141 WKVQRRAAH
408 SVLGYHIPK	150 SMMRNFFTR	312 GARLDLENV	128 GGRSMAFGH
404 TANTSVLGY	149 HSMMRNFFT	287 AAPRDMMDA	122 SFRVVSGGR
398 TIPHATTAN	130 RSMAGHYS	279 HCESLRPGA	96 VLINGERAH
374 DQPNL PYVL	106 ALVQQGSAF	242 DVMPWLQYF	73 SFARLARRY
370 PCMGDQPNL	80 RYGDVFQIR	199 VAVANVMSA	68 QAAHLSFAR
364 VGRDRLPCM	55 FAWPLIGNA	196 LTVVAVANV	66 VGQAAHLSF
361 DQVVGRDRL	54 PFAWPLIGN	182 VRGSADGAF	42 QRRRQLRSA
359 ELDQVVGRD	6 SPNDPWPLN	149 HSMMRNFFT	30 LATVHVGQR
348 RYDPDVQTRV	529 LDSAVQNLQ	147 AAHSMMRNF	522 LRESMELL
346 FTRYPPDVQ	524 ESMELLDSA	140 HWKVQRRAA	518 VNVTLRESM
324 ITDIFGASQ	511 IKPKSFKVN	139 EHWKVQRRA	503 MNFSYGLTI
303 KAAGDSHGG	507 YGLTIKPKS	111 GSAFADRPA	486 ILAHQCDFR
290 RDMMDAFIL	494 RANPNEPAK	107 LVQQGSAFA	478 MQLFLFISI
276 FLRHCESLR	488 AHQCDFRAN	94 IVVLNGERA	475 LSKMQLFLF
263 QLNRRNFSNF	484 ISILAHQCD	76 RLARRYGDV	453 NKDLTSRVM

243 VMPWLQYFP	468 RRCIGEELS	70 AHLSFARLA	440 FDPARFLDK
223 ELLSHNEEF	460 VMIFSVGKR	42 QRRRQLRSA	405 ANTSVLGYH
189 AFLDPRPLT	457 TSRVMIFSV	23 LLLLLSVLA	404 TANTSVLGY
163 RQVLEGHVL	432 LKWPNPENF	21 TLLLLLSV	360 LDQVVGRDR
117 RPAFASFRV	420 VFVNQWSVN	10 PWPLNPLSI	348 RYPDVTQTRV
113 AFADRPAFA	409 VLGYHIPKD	525 SMELLDASV	334 TLSTALQWL
100 ERAIHQALV	373 GDQPNLPYV	510 TIKPKSFKV	320 VPATITDIF
71 HLSFARLAR	371 CMGDQPNLP	502 KMNFSYGLT	319 NVPATITDI
67 GQAAHLSFA	367 DRLPCMGDQ	497 PNEPAKMNF	288 APRDMMDAF
62 NAAAVGQAA	358 AELDQVVG	485 SILAHQCDF	276 FLRHCESLR
61 GNAAAVGQA	321 PATITDIFG	478 MQLFLFISI	251 PNPVRTVFR
57 WPLIGNAAA	298 LSAEKKAAG	473 EELSKMQLF	225 LSHNEEFGR
49 SAPPGPFAW	276 FLRHCESLR	455 DLTSRVMIF	217 DDPEFRELL
12 PLNPLSIQQ	263 QLNRNFSNF	444 RFLDKDGLI	206 SAVCFGCRY
495 ANPNEPAKM	249 YFPNPVRTV	437 PENFDPARF	162 SRQVLEGHV
487 LAHQCDFRA	248 QYFPNPVRT	432 LKWPNPENF	155 FFTRQPRS
482 LFISILAHQ	245 PWLQYFPNP	401 HATTANTS	152 MRNFFTRQP
472 GEELSKMQL	242 DVMPWLQYF	394 FVPVTIPHA	150 SMMRNFFTR
448 KDGLINKDL	237 AGSLVDVMP	380 YVLAFLYEA	134 FGHYSEHWK
438 ENFDPARFL	231 FGRTVGAGS	372 MGQPNLPY	109 QGSAFADR
431 PLKWPNPEN	225 LSHNEEFGR	344 LLFTRYPDV	77 LARRYGDVF
426 SVNHDPWKW	194 RPLTVVAVA	316 DLENPATI	71 HLSFARLAR
424 QWSVNHDP	178 VALLVRGSA	281 ESLRPGAAP	5 LSPNDPWPL
399 IPHATTANT	164 QVLEGHVLS	263 QLNRNFSNF	476 SKMQLFLFI
390 RFSSFVPT	157 TRQPRSRQV	260 EFEQLNRF	463 FSVGKRRCI
382 LAFLYEAMR	131 SMAFGHYSE	246 WLQYFPNPV	424 QWSVNHDP
371 CMGDQPNLP	122 SFRVVSGGR	227 HNEEFGR	364 VGRDRLPCM
368 RLPCMGDQP	118 PAFASFRVV	226 SHNEEFGR	254 VRTVFREFE
298 LSAEKKAAG	111 GSAFADRP	223 ELLSHNEEF	222 RELLSHNEE
287 AAPRDMMDA	97 LNGERAIHQ	178 VALLVRGSA	214 YSHDDPEFR
265 NRNFNSNFI	96 VLNGERAIH	166 LEGHVLSEA	205 MSAVCFGCR
242 DVMPWLQYF	82 GDVFQIRLG	157 TRQPRSRQV	194 RPLTVVAVA
204 VMSAVCFG	72 LSFARLARR	119 AFASFRVVS	143 VQRRAAHSM
192 DPRPLTVVA	69 AAHLSFARL	95 VVLNGERAI	95 VVLNGERAI
158 RQPRSRQVL	64 AAVGQAAHL	78 ARRYGDVFQ	86 QIRLGSCPI
94 IVVLNGERA	51 PPGPFAWPL	55 FAWPLIGNA	450 GLINKDLT
51 PPGPFAWPL	38 RLLRQRRRQ	52 PGPFAWPLI	447 DKDGLINKD
48 RSAPPGPFA	32 TVHVGQRL	25 LLLSVLATV	391 FSSFVPTI
42 QRRRQLRSA	29 VLATVHVGQ	533 VQNLQAKET	381 VLAFLYEAM
13 LNPLSIQQT	28 SVLATVHVG	508 GLTIKPKSF	316 DLENPATI
509 LTIKPKSF	27 LSVLATVHV	487 LAHQCDFRA	301 EKKAAGDSH
505 FSYGLTIKP	5 LSPNDPWPL	480 LFLFISILA	285 PGAAPRDM
494 RANPNEPAK	533 VQNLQAKET	475 LSKMQLFLF	168 GHVLSEARE
459 RVMIFSVGK	532 AVQNLQAKE	449 DGLINKDLT	135 GHYSEHWKV
447 DKDGLINKD	521 TLRESMELL	419 VVFVNQWSV	101 RAIHQALVQ
417 DTVVFVNQW	500 PAKMNFSY	410 LGYHIPKD	45 RQLRSAPPG
396 PVTIPHATT	495 ANPNEPAKM	366 RDRLPCM	41 RQRRRQLRS
388 AMRFSSFVP	493 FRANPNEPA	296 FILSAEKKA	10 PWPLNPLSI
347 TRYPDVQTR	486 ILAHQCDFR	285 PGAAPRDM	505 FSYGLTIKP
340 QWLLLLFTR	464 SVGKRRCIG	268 FSNFILDKF	412 YHIPKDTVV
323 TITDIFGAS	461 MIFSVGKRR	237 AGSLVDVMP	406 NTSVLGYHI
299 SAEKKAAGD	435 PNPNFDPA	185 SADGAFLDP	314 RLDLENVPA
294 DAFILSAEK	431 PLKWPNPEN	162 SRQVLEGHV	266 RNFSNFI
291 DMMDAFILS	423 NQWSVNHDP	156 FTRQPRSRQ	264 LNRNFSNFI
286 GAAPRDMMD	418 TVVFNQWS	135 GHYSEHWKV	233 RTVGAGSLV
248 QYFPNPVRT	405 ANTSVLGYH	105 QALVQQGSA	154 NFFTRQPRS
229 EEFGRTVGA	389 MRFSSFVPV	98 NGERAIHQA	146 RAAHSMMRN
226 SHNEEFGR	377 NLPYVLAFL	71 HLSFARLAR	38 RLLRQRRRQ
203 NVMSAVCFG	375 QPNLPYVLA	13 LNPLSIQQT	532 AVQNLQAKE

198 VVAVANVMS	362 QVVGRDRLP	523 RESMELLDs	523 RESMELLDs
197 TVVAVANVM	361 DQVVGRDRL	509 LTIKPKSK	507 YGLTIKPKS
195 PLTVVAVAN	360 LDQVVGRDR	469 RCIGEELSK	491 CDFRANPNE
185 SADGAFLDP	352 VQTRVQAEI	445 FLDKDGLIN	466 GKRRRCIGEE
151 MMRNFFTRQ	323 TITDIFGAS	433 KWPNPENFD	419 VVFVNQWSV
132 MAFGHYSEH	306 GDSHGGGAR	392 SSFVPVTIP	397 VTIPHATTA
112 SAFADRPAF	296 FILSAEKKA	388 AMRFSSFVP	392 SSFVPVTIP
90 GSCPIVVLN	295 AFILSAEKK	363 VVGRDRLPC	390 RFSSFVPVT
72 LSFARLARR	285 PGAAPRDMM	358 AELDQVVGR	366 RDRLPCMGD
70 AHLSFARLA	257 VFREFEQLN	282 SLRPGAAPR	355 RVQAELDQV
34 HVGQRLLRQ	256 TVFREFEQL	247 LQYFPNPVR	329 GASQDTLST
30 LATVHVGQR	247 LQYFPNPVR	241 VDVMPPWLQY	325 TDIFGASQD
20 QTLLLILS	217 DDPEFRELL	234 TVGAGSLVD	312 GARLDLENV
518 VNVTLRESM	208 VCFGCRYSH	186 ADGAFLDPR	311 GGARLDLEN
493 FRANPNEPA	207 AVCFGCRYS	165 VLEGHVLSE	278 RHCESLRPG
461 MIFSVGKRR	204 VMSAVCFGC	160 PRSRQVLEG	248 QYFPNPVRT
446 LDKDGLINK	200 AVANVMSAV	120 FASFRVVSG	245 PWLQYFPNP
441 DPARFLDKD	198 VVAVANVMS	114 FADRPAFAS	238 GSLVDVMPW
421 FVNQWSVNH	197 TVVAVANVM	63 AAAVGQAAH	139 EHWKVQRR
403 TTANTSVLG	195 PLTVVAVAN	43 RRRQLRSAP	121 ASFRVVSGG
392 SSFVPVTIP	180 LLVRGSAVG	41 RQRRQLRS	117 RPAFASFRV
376 PNLPYVLA	179 ALLVRGSAVG	33 VHVGQRLLR	90 GSCPIVVLN
375 QPNLPYVLA	173 EARELVALL	511 IKPKSFKVN	83 DVFQIRLG
351 DVQTRVQAE	155 FTRQPRSR	494 RANPNEPAK	82 GDVFQIRLG
317 LENVPATIT	151 MMRNFFTRQ	488 AHQCDFRAN	55 FAWPLIGNA
304 AAGDSHGGG	140 HWKVQRRRAA	459 RVMIFSVGK	53 GPFIAWPLIG
259 REFEQLNRN	138 SEHWKVQRR	440 FDPARFLDK	52 PGPFAWPLI
201 VANVMSAVC	124 RVVSGGRSM	431 PLKWPNPEN	48 RSAPPGPFA
143 VQRRAAHSM	119 AFASFRVVS	416 KDTVVFVNQ	21 TTLLLILS
121 ASFRVVSGG	112 SAFADRPAF	324 ITDIFGASQ	534 QNLQAKETC
115 ADRPAFASF	109 QQGSAFADR	306 GDSHGGGAR	527 ELLDSAVQN
98 NGERAIHQAA	95 VVLNGERAI	303 KAAGDSHGG	526 MELLDLSAVQ
93 PIVVNLNGER	78 ARRYGDFVQ	267 NFSNFIIDK	512 KPKSFKVN
92 CPIVVLNGE	77 LARRYGDFV	251 PNPNRTVFR	462 IFSGVKRR
68 QAAHLSFAR	70 AHLSFARLA	231 FGRTVGAGS	416 KDTVVFVNQ
56 AWPLIGNAA	65 AVGQAAHLS	230 EFGRTVGAG	411 GYH1PKDTV
14 NPLSIQQTT	63 AAAVGQAAH	215 SHDDPEFRE	409 VLGYH1PKD
10 PWPLNPLSI	62 NAAAVGQAA	179 ALLVRGSAVG	373 GDQPNLPYV
533 VQNLQAKET	57 WPLIGNAAA	176 ELVALLVRG	359 ELDQVVGRD
507 YGLTIKPKS	40 LRQRRRQLR	175 RELVALLVR	326 DIFGASQDT
480 LFLFISILA	25 LLLSVLATV	151 MMRNFFTRQ	322 ATITDIFGA
469 RCIGEELSK	23 LLLLSSVLA	130 RSMAFGHYS	302 KKAAGDSHG
466 GKRRRCIGEE	15 PLSIQQTTL	102 AIHQALVQQ	286 GAAPRDMM
395 VPVTIPHAT	531 SAVQNLQAK	101 RAIHQALVQ	255 RTVFREFEQ
313 ARLDLENVP	518 VNVTLRESM	96 VLNGERAIH	229 EEFGRVG
311 GGARLDLEN	513 PKSFKVNVT	90 GSCPIVVLN	184 GSADGAFLD
305 AGDSHGGGA	506 SYGLTIKPK	75 ARLARRYGD	176 ELVALLVRG
289 PRDMMDAFI	504 NFSYGLTIK	60 IGNAAAVGQ	164 QVLEGHVL
268 FSNFILDKF	502 KMNFSYGLT	54 PFAWPLIGN	156 FTRQPRSRQ
238 GSLVDVMPW	496 NPNEPAKMN	26 LLSVLATVH	107 LVQQGSAFA
234 TVGAGSLVD	485 SILAHQCDF	7 PNDPWPLNP	102 AIHQALVQQ
208 VCFGCRYSH	473 EELSKMQLF	4 SLSPNDPWP	88 RLGSPIVV
207 AVCFGCRYS	470 CIGEELSKM	3 TSLSPNDPWP	58 PLIGNAAAV
206 SAVCFGCRY	462 IFSGVKRR	532 AVQNLQAKE	57 WPLIGNAAA
186 ADGAFLDPR	455 DLTSRVMIF	529 LDSAVQNLQ	34 HVGQRLLRQ
175 RELVALLVR	454 KDLTSRVM	527 ELLDSAVQN	25 LLLSVLATV
142 KVQRRAAHS	449 DGLINKDLT	516 FKVNVTLRE	24 LLLLSSVLA
138 SEHWKVQRR	444 RFLDKDGLI	505 FSYGLTIK	23 LLLLSSVLA
119 AFASFRVVS	441 DPARFLDKD	504 NFSYGLTIK	14 NPLSIQQTT

114 FADRP AFA S	427 VNHDPLKWP	495 ANPNEPAKM	13 LNPLSIQQT
103 IHQALVQQG	422 VNQWSVNH D	492 DFRANPNEP	2 GTSLSPNDP
101 RAIHQALVQ	390 RFSSFVPT	486 ILAHQCDFR	516 FKVNVTLRE
91 SCPIVVLNG	388 AMRFSSFVP	481 FLFISILAH	511 IKPKSFKVN
84 VFQIRLGSC	384 FLYEAMRFS	464 SVGKRCIG	510 TIKPKSFKV
77 LARRYGDVF	382 LAFLYEA MR	462 IFSVGKRC	487 LAHQCDFRA
65 AVGQAAHLS	381 VLAFLYEA M	456 LTSRVMIFS	482 LFISILAHQ
50 APPGPFAWP	380 YVLAFLYEA	447 DKDGLINKD	480 LFLFISILA
11 WPLNPLSIQ	369 LPCMGDQPN	439 NFDPARFLD	452 INKDLTSRV
530 DSAVQNLQA	368 RLPCM GDQ P	428 NHDPWKWP N	430 DPLKWPNP E
513 PKSFKVNV T	356 VQAELDQVV	427 VNHDPLKWP	429 HDPLKWPNP
464 SVGKRCIG	348 RYPDVQTRV	415 PKDTVVFVN	380 YVLAFLYEA
456 LTSRVMIFS	345 LFTRYPDVQ	408 SVLGYHIPK	368 RLPCM GDQ P
427 VNHDPLKWP	343 LLLFTRYPD	404 TANTSVLGY	357 QAEILDQVVG
422 VNQWSVNH D	332 QDTLSTALQ	403 TTANTSVLG	350 PDVQTRVQA
410 LGYHIPKDT	325 TDIFGASQD	398 TIPHATTAN	333 DTLSTALQW
393 SFVPVTIPH	313 ARLDLENVP	393 SFVPVTIPH	315 LDLENVPAT
386 YEAMRFSSF	310 GGGARLDLE	379 PYVLAFLYE	308 SHGGGARLD
363 VVGRDRRLPC	302 KKAAGDSHG	364 VGRDRRLPCM	303 KAAGDSHGG
362 QVVGDRRLP	270 NFILDKFLR	359 ELDQVVG RD	299 SAEKKAAGD
333 DTLSTALQW	269 SNFILDKFL	357 QAEILDQVVG	292 MMAFILSA
308 SHGGGARLD	261 FEQLNRNFS	318 ENVPATITD	274 DKFLRH CES
295 AFILSAEKK	259 REFEQLNRN	313 ARLDLENVP	237 AGSLV DVMP
293 MDAFILSAE	254 VRTVFREFE	311 GGARLDLEN	235 VGAGSLV DV
279 HCESLRPG A	244 MPWLQYFPN	308 SHGGGARLD	234 TVGAGSLVD
278 RHCESLRPG	236 GAGSLV DVM	304 AAGDSHGGG	228 NEEFGR TVG
267 NFSNFI LDK	235 VGAGSLV DV	302 KKAAGDSHG	196 LTVVAVANV
240 LVDVMPW LQ	232 GRTVGAGSL	301 EKKAAGD SH	191 LDPRPLTVV
184 GSADGAFLD	223 ELLSHNEEF	300 AEKKAAGDS	189 AFLDPRPLT
171 LSEARELVA	210 FGC RYSHDD	298 LSAEKKAAG	187 DGAFLDPRP
156 FTRQPRSRQ	201 VANVMSAVC	283 LRPGAAPRD	180 LLVRGSA
147 AAHSMMRN F	199 VAVANVMSA	272 ILDKFLRH C	178 VALLVRGSA
146 RAAHSMMRN	191 LDPRPLTVV	271 FILDKFLRH	165 VLEGHVLSE
111 GSAFADRP A	172 SEARELVAL	236 GAGSLV DVM	125 VVSGGRSMA
83 DVFQIRLGS	166 LEGHVLSEA	228 NEEFGR TVG	118 PAFASFRVV
75 ARLARRYGD	163 RQVLEGHVL	224 LLSHNEEFG	105 QALVQQGSA
60 GNAAA AVGQ	162 SRQVLEGH V	220 EFRELLSHN	94 IVVLNGERA
35 VGQRLLRQR	159 QPRSRQVLE	208 VCFG CRYSH	92 CPIVVLNG E
6 SPNDPWPLN	158 RQPRSRQVL	204 VMSAVCFG C	91 SCPIVVLNG
2 GTSLSPNDP	148 AHSMMRNFF	203 NVMSAVCFG	67 QAAHLSFA
523 RESMELLDS	139 EHWKVQRR A	198 VVAVANVMS	61 GNAAA AVGQA
515 SFKVNVTLR	135 GHYSEHWKV	195 PLTVVAVAN	50 APPGPFAWP
506 SYGLTIKP K	133 AFGHYSEHW	161 RSRQVLEGH	12 PLNPLSIQ
504 NFSYGLTIK	127 SGGRSMAFG	153 RNFFTRQPR	11 WPLNPLSIQ
475 LSKMQLFLF	123 FRVVS GGRS	145 RRAAHSM MR	1 MGTSLS PND
449 DGLINKDLT	120 FASFRV VSG	144 QRRAAHSM M	529 LDAVQNLQ
432 LKWPNPENF	108 VQQGSAFAD	141 WKVQRR AAH	525 S MELLDS A
405 ANTSVLGYH	107 LVQQGSAFA	136 HYSEHWKVQ	524 ESMELLDS A
357 QAEILDQVVG	105 QALVQQGSA	133 AFGHYSEHW	517 KVNVTLRES
320 VPATITDIF	104 HQALVQQGS	129 GRSMAFGHY	513 PKSFKVNV T
310 GGGARLDLE	100 ERAIHQALV	127 SGGRSMAFG	484 ISILAHQCD
302 KKAAGDSHG	92 CPIVVLNG E	121 ASFRV VSGG	477 KMQLFLFIS
283 LRPGAAPRD	89 LGSCPIVVL	110 QGSAFADRP	471 IGEELSKMQ
280 CESLRPGAA	86 QIRLGSCPI	109 QQGSAFADR	457 TS RVMIFS V
255 RTVFREFEQ	85 FQIRLGSCP	108 VQQGSAFAD	433 KWPNPENFD
222 RELLSHNEE	79 RRYGDVFQI	103 IHQALVQQG	431 PLKWPNPEN
219 PEFRELLSH	75 ARLARRYGD	91 SCPIVVLNG	428 NHDPWKWP N
161 RSRQVLEGH	74 FARLARRYG	83 DVFQIRLGS	417 DTVVFVNQW
149 HSMMRNFFT	58 PLIGNAAA V	80 RYGDVFQIR	407 TSVLGYHIP

78 ARR YGDVFQ	56 AWPLIGNAA	74 FARLARRYG	401 HATTANTS V
74 FARLARRYG	52 PGPF AWPLI	65 AVGQAAHLS	399 IPHATTANT
73 SFARLARRY	42 QRRRQLRSA	59 LIGNAAA AVG	394 FVPVTIPHA
54 PFAWPLIGN	39 LLRQRRRQL	46 QLRSAPP GP	388 AMRFSSFVP
52 PGPF AWPLI	26 LLSVLATVH	45 RQLRSAPP G	362 QVVGRDRLP
534 QNLQAKETC	22 TLLLLLSVL	44 RRQLRSAPP	356 VQAELDQVV
526 MELLD SAVQ	535 NLQAKETCQ	36 GQRLLRQRR	346 FTRYPDVQT
516 FKVNVTLRE	527 ELLDSAVQN	34 HVGQRLLRQ	344 LLFTRYPDV
489 HQCDFRANP	526 MELLD SAVQ	29 VLATVHVGQ	339 LQWLLLLFT
484 ISILAHQCD	519 NVTLRESME	28 SVLATVHVG	330 ASQDTLSTA
462 1FSVGKRRC	508 GLTIKP KSF	535 NLQAKETCQ	318 ENVPATITD
453 NKDLTSRVM	501 AKMNF SYGL	526 MELLD SAVQ	317 LENVPATIT
378 LPYVLAFLY	491 CDFRANPNE	522 LRESMELLD	310 GGGARLDLE
369 LPCMGDQPN	489 HQCDFRANP	515 SFKVNVTLR	300 AEKKAAGDS
353 QTRVQAELD	483 FISILAHQC	506 SYGLTIKPK	298 LSAEKKAAG
349 YPDVQTRVQ	479 QLFLFISIL	498 NEPAKM NFS	296 FILSAEKKA
306 GDSHGGAR	467 KRR CIGEEL	490 QCDFRANPN	281 ESLRPGAAP
288 APRDMMDAF	448 KDG LINKDL	489 HQCDFRANP	272 ILDKFLRHC
285 PGAAPRDMM	443 ARFLDKDGL	483 FISILAHQC	262 EQLNRNF SN
284 RPGAAPRDM	438 ENFDPARFL	466 GKRR CIGEE	252 NPVRTVFRE
257 VFREFEQLN	433 KWPNPENFD	458 SRVMIFS V	243 VMPWLQYFP
252 NPVRTVFRE	421 FVNQWSVNH	453 NKDLTSRVM	226 SHNEEFGR
250 FPNPVRTVF	419 VVFVNQWSV	451 LINKDLTSR	220 EFRELLSHN
247 LQYFPNPVR	414 IPKDTVVVF	450 GLINKDLTS	211 GCRYSHDDP
237 AGSLVDVMP	413 HIPKDTVVF	442 PARFLDKDG	199 VAVANVMSA
231 FGRTVGAGS	411 GYHIPKDTV	426 SVNHDPLKW	192 DPRPLTVVA
220 EFRELLSHN	401 HATTANTS V	421 FVNQWSVNH	181 LVRGSADGA
215 SHDDPEFRE	396 PVTIPHATT	409 VLGYHIPKD	179 ALLVRGSA
202 ANVMSAVCF	395 VPV TIPHAT	405 ANTSVLGYH	166 LEGHVLSEA
160 PRSRQVLEG	394 FVPVTIPHA	385 LYEA MRFSS	151 MMRNFFTRQ
144 QRRAAHSM	383 AFLYEAMRF	381 VLAFLYEA M	142 KVQRRAAHS
140 HWKVQRRAA	374 DQPNLPYVL	368 RLPCM GDQP	131 SMAFGHYS
127 SGGRSM AFG	370 PCMGDQPNL	362 QVVGRDRLP	130 RSMAGHYS
126 VSGGRSM AFG	366 RDRLPCM GD	354 TRVQAELDQ	111 GSAFADRP A
108 VQQGSAFAD	364 VGRDRLPCM	353 QTRVQAELD	108 VQQGSAFAD
97 LNGERAIHQ	351 DVQTRVQAE	351 DVQTRVQAE	104 HQALVQQGS
85 FQIRLGSCP	350 PDVQTRVQA	347 TRYPDVQTR	103 IHQALVQQG
82 GDVFQIRLG	344 LLFTRYPDV	343 LLLFTRYPD	98 NGERAIHQ A
66 VGQAAHLSF	342 LLLLFTTRY	341 WLLLLFTRY	85 FQIRLGSCP
33 VHVGQRLLR	334 TLSTALQW	333 DTLSTALQW	76 RLARRYGDV
9 DPWPLNPLS	326 DIFGASQDT	332 QDTLSTALQ	70 AHLSFARLA
529 LDSAVQNLQ	320 VPATITDIF	328 FGASQDTLS	65 AVGQAAHLS
519 NVTLRESME	317 LENVPATIT	323 TITDIFGAS	56 AWPLIGNAA
496 NPNEPAKMN	315 LDLENVPAT	310 GGGARLDLE	28 SVLATVHVG
488 AHQCDFRAN	304 AAGD SHGG	299 SAEKKAAGD	20 QTLLLLS
471 IGEELSKMQ	303 KAAGD SHGG	295 AFILSAEK	9 DPWPLNPLS
435 PNPENFDPA	301 EKKAAGD SH	293 MDAFILSAE	7 PNDPWPLNP
434 WPNPENFDP	300 AEKKAAGDS	291 DMMDAFILS	3 TSLSPNDPW
433 KWPNPENFD	297 ILSAEKKA	286 GAAPRDMM D	535 NLQAKETCQ
428 NHDPLKWPN	288 APRDMMDAF	278 RH CESLRPG	533 VQNLQAKET
418 TVVFVNQWS	287 AAPRDMMDA	277 LRH CESLRP	530 DSAVQNLQA
407 TSVLGYHIP	283 LRPGAAPRD	276 FLRH CESLR	502 KMNFSYGLT
385 LYEA MRFSS	273 LDKFLRHCE	266 RNFSNFI LD	496 NPNEPAKMN
383 AFLYEAMRF	265 NRNF SNFIL	261 FEQLNRNFS	489 HQCDFRANP
367 DRLPCM GDQ	262 EQLNRNFSN	258 FREFEQLNR	483 FISILAHQC
350 PDVQTRVQA	252 NPVRTVFRE	257 VREFEQLN	449 DGLINKDLT
332 QDTLSTALQ	246 WLQYFPNPV	254 VRTVFREFE	445 FLDKDG LIN
328 FGASQDTLS	243 VMPWLQYFP	245 PWLQYFPNP	441 DPARFLDKD
325 TDI FGASQD	230 EFGRTVGAG	238 GSLVDVMPW	434 WPNPENFD P

318 ENVPATITD	229 EEFGRTVGA	219 PEFRELLSH	426 SVNHDPLKW
281 ESLRPGAAP	224 LLSHNEEFG	211 GCRYSHDDP	422 VNQWSVNH
277 LRHCESLRP	203 NVMSAVCFG	207 AVCFGCrys	420 VFVNQWSVN
253 PVRTVFREF	202 ANVMSAVCF	205 MSAVCFGCR	418 TVVFVNQWS
241 VDVMPPWLQY	193 PRPLTVVAV	201 VANVMSAVC	415 PKDTVVFVN
225 LSHNEEFGR	186 ADGAFLDPR	197 TVVAVANVM	414 IPKDTVVFV
214 YSHDDPEFR	183 RGSADGAFL	187 DGAFLDPRP	410 LGYHIPKDT
213 RYSHDDPEF	182 VRGSADGAF	177 LVALLVRGS	400 PHATTANTS
210 FGCRYSHDD	181 LVRGSADGA	167 EGHVLSEAR	396 PVTIPHATT
168 GHVLSEARE	177 LVALLVRGS	164 QVLEGHVL	384 FLYEAMRFS
152 MRNFFTRQP	176 ELVALLVRG	150 SMMRNFTR	379 PYVLAFLYE
148 AHSMMRNFF	153 RNFFTRQPR	146 RAHSMMRN	375 QPNLPYVLA
141 WKVQRRAAH	147 AAHSMMRNF	143 VQRRAAHSM	369 LPCMGDQPN
137 YSEHWKVQR	145 RRAHSMMR	142 KVQRRAAHS	343 LLLFTRYPD
133 AFGHYSEHW	144 QRRRAHSMM	137 YSEHWKVQR	342 LLLLFTTRYP
130 RSMAFGHYS	143 VQRRAAHSM	132 MAFGHYSEH	332 QDTLSTALQ
122 SFRVVSGGR	141 WKVQRRAAH	128 GGRSMAFGH	328 FGASQDTLS
104 HQALVQQGS	136 HYSEHWKVQ	124 RVVSGGRSM	324 ITDIFGASQ
53 GPFAWPLIG	134 FGHYSEHWK	122 SFRVVSGGR	297 ILSAEKKA
47 LRSAPPGPF	132 MAFGHYSEH	116 DRPAFASFR	293 MDAFILSAE
45 RQLRSAPPG	113 AFADRPAFA	72 LSFARLARR	249 YFPNPVRTV
3 TSLSPNDPW	103 IHQALVQQG	68 QAAHLSFAR	215 SHDDPEFRE
522 LRESMELLD	102 AIHQALVQQ	49 SAPPGPFAW	207 AVCFGCrys
498 NEPAKMNF	94 IVVLNGERA	38 RLLRQRRQ	201 VANVMSAVC
492 DFRANPNEP	93 PIVVLNGER	20 QTTLLLLS	200 AVANVMSAV
491 CDFRANPNE	87 IRLGSCPIV	2 GTSLSPNDP	195 PLTVVAVAN
468 RRCIGEELS	84 VFQIRLGSC	531 SAVQNLQAK	190 FLDPRPLTV
458 SRVMIFSVG	76 RLARRYGDV	518 VNVTLRESM	185 SADGAFLDP
440 FDPARFLDK	61 GNAAVGQA	517 KVNVTLRES	177 LVALLVRGS
439 NFDPARFLD	59 LIGNAAAVG	507 YGLTIKPKS	159 QPRSRQVLE
436 NPENFDPAR	47 LRSAPPGP	500 PAKMNFSY	120 FASFRVVSG
430 DPLKWPNE	46 QLRSAPPGP	491 CDFRANPNE	119 AFASFRVVS
429 HDPLKWPNP	43 RRRQLRSAP	484 ISILAHQCD	110 QGSAFADRP
423 NQWSVNHDP	36 GQRLLRQRR	482 LFISILAHQ	97 LNGERAIHQ
416 KDTVVFVNQ	35 VGQRLLRQR	477 KMQLFLFIS	60 IGNAAAVGQ
400 PHATTANTS	30 LATVHVQQR	471 IGEELSKMQ	59 LIGNAAAVG
372 MGDQPNLPY	11 WPLNPLSIQ	470 CIGEELSKM	54 PFAWPLIGN
366 RDRLPCMGD	8 NDPWPLNPL	468 RRCIGEELS	49 SAPPGPFAW
365 GRDRLPCMG	HLA-A1 Decamers	461 MIFSVGKRR	27 LSVLATVHV
360 LDQVVGRDR	Pos 1234567890	460 VMIFSVGKR	4 SLSPNDPWP
345 LFTRYPDVQ		429 HDPLKWPNP	519 NVTLRESME
274 DKFLRHCES		425 WSVNHDPLK	498 NEPAKMNF
273 LDKFLRHCE	240 LVDVMPWLQY	422 VNQWSVNH	492 DFRANPNEP
270 NFIKFLKFLR	403 TTANTSVLGY	420 VFVNQWSVN	490 QCDFRANPN
261 FEQLNRNFS	439 NFDPARFLDK	417 DTVVFVNQW	464 SVGKRRRCIG
230 EFGRTVGAG	371 CMGDQPNLPY	400 PHATTANTS	456 LTSRVMIFS
221 FRELLSHNE	205 MSAVCFGCR	384 FLYEAMRFS	442 PARFLDKDG
205 MSAVCFGCR	72 LSFARLARRY	382 LAFLYEAMR	427 VNHDPLKWP
187 DGAFLDPRP	377 NLPYVLAFLY	371 CMGDQPNLP	423 NQWSVNHDP
182 VRGSADGAF	340 QWLLLLFTTRY	367 DRDRLPCMG	403 TTANTSVLG
159 QPRSRQVLE	174 ARELVALLVR	365 GRDRLPCMG	398 TIPHATTAN
155 FFTRQPRSR	128 GGRSMAFGHY	360 LDQVVGRDR	395 VPVTIPHAT
154 NFFTRQPRS	216 HDDPEFRE	345 LFTRYPDVQ	387 EAMRFSSFV
145 RRAHSMMR	190 FLDPRPLTVV	342 LLLLFTTRYP	321 PATITDIFG
139 EHWKVQRRA	137 YSEHWKVQRR	321 PATITDIFG	304 AAGDSHGGG
128 GGRSMAFGH	522 LRESMELLD	294 DAFILSAEK	287 AAPRDMMDA

109 QQGSAFADR	498 NEPAKMNFSY	273 LDKFLRHCE	279 HCESLRPGA
44 RRQLRSAPP	445 FLDKDGLINK	262 EQLNRNFSN	261 FEQLNRNFS
43 RRRQLRSAP	336 STALQWLLLL	259 REFEQLNRM	231 FGRTVGAGS
40 LRQRRLRQLR	324 ITDIFGASQD	255 RTVFREFEQ	227 HNEEFGRTV
37 QRLLRQRR	218 DPEFRELLSH	243 VMPWLQYFP	198 VVAVANVMS
36 GQRLLRQRR	215 SHDDPEFREL	240 LVDVMPWLQ	171 LSEARELVA
511 IKPKSFKVN	90 GSCPIVVLNG	222 RELLSHNEE	136 HYSEHWKVQ
499 EPAKMNF SY	497 PNEPAKMNF S	214 YSHDDPEFR	133 AFGHYSEHW
465 VGKRR CIGE	428 NHDPLKWPNP	212 CRYSHDDPE	127 SGGRSMAFG
425 WSVNH DPLK	331 SQDTLSTALQ	209 CFGCRYSHD	114 FADRPAFAS
420 VFVNQWSVN	233 RTVGAGSLVD	206 SAVCFGCRY	113 AFADRPAFA
415 PKDTVVFVN	171 LSEARELVAL	184 GSADGAFLD	84 VFQIRLGSC
354 TRVQAELDQ	114 FADRPAFASF	180 LLVRGSADG	29 VLATVHVGQ
300 AEKKAAGDS	81 YGDVFQIRLG	168 GHVLSEARE	6 SPNDPWPLN
266 RNFSN FILD	7 PNDPWPLNPL	154 NFFTRQPRS	500 PAKMNFSY G
262 EQLNRNFSN	528 LLDSAVQNLQ	152 MRNFFTRQP	488 AHQCDFRAN
254 VRTVFR EFE	525 SMELLD SAVQ	138 SEHWKVQRR	465 VGKRR CIGE
251 PNPVRTVFR	475 LSKMQLFLFI	131 SMAFGHYSE	439 NFDPARFLD
245 PWLQYFPNP	415 PKDTVVFVNQ	123 FRVVSGGRS	435 PN PENFDPA
244 MPWLQYFPN	385 LYEA MRFSSF	104 HQALVQQGS	385 LYEA MRFSS
212 CRYSHDDPE	349 YPDVQTRVQA	97 LNGERAHQ	371 CMGDQPNLP
136 HYSEHWKVQ	185 SADGAFLDPR	85 FQIRLGSCP	363 VVGRDRLPC
134 FGHYSEHWK	184 GSADGAFLDP	73 SFARLARRY	353 QTRVQAELD
129 GRSMAFGHY	165 VLEGHVLSEA	40 LRQRRLRQLR	351 DVQTRVQAE
123 FRVVSGGRS	472 GEELSKMQLF	30 LATVHVGQR	349 YPDVQTRVQ
110 QGSAFADRP	453 NKDLTSRVMI	12 PLNPLSIQQ	345 LFTRYPDVQ
80 RYGDVFQIR	447 DKDGLINKDL	1 MGTSLSPND	323 TITDIFGAS
41 RQRRRQLRS	425 WSVNH DPLK		305 AGD SHGGGA
1 MGTSLSPND	359 ELDQVVGRDR	HLA-B*0702 Decamers	291 DMMDAFILS
437 PENFDPARF	353 QTRVQAELDQ	Pos 1234567890	280 CESLRPGAA
167 EGHVLSEAR	335 LSTALQWLLL	50 APPGPFAWPL	273 LDKFLRHCE
497 PNEPAKMNF	314 RLDLENVPAT		257 VFREFEQLN
379 PYVLAFLYE	305 AGD SHGGGA		
301 EKKAAGD SH	299 SAEKKAAGDS	192 DPRPLTVVAV	246 WLQYFPNPV
218 DPEFRELLS	272 ILDKFLRHCE	288 APRDMMDAFI	244 MPWLQYFPN
260 EFEQLNRNF	227 HNEEFGRTVG	369 LPCMGDQPNL	240 LVDVMPWLQ
	20 QTTLLLLSV	14 NPLSIQQTTL	230 EFGRTVGAG
		375 QPNLPYVLA F	218 DPEFRELLS
HLA-A*0201 Decamers	16 LSIQQTLLL	349 YPDVQTRVQA	210 FGCRYSHD
Pos 1234567890	490 QCDFRANPNE	284 RPGAAPRDMM	209 CFGCRYSHD
24 LLLL SVLATV	397 VTIPHATTAN	117 RPAFASFRVV	204 VMSAVCFG C
190 FLDPRPLTVV	357 QAEQDQVVG R	512 KPKSFKVNVT	203 NVMSAVCFG
88 RLGSCPIVVL	316 DLENVPATIT	434 WPNPENFDPA	170 VLSEAREL V
17 SIQQTLLL	260 EFEQLNRNF S	51 PPGPFAWPLI	149 HSMMRNFFT
527 ELLD SAVQNL	258 FREFEQLNRM	9 DPWPLNPLSI	74 FARLARRY G
413 HIPKDTVVFV	221 FRELLSHNEE	57 WPLIGNAAAV	62 NAAAVGQAA
343 LLLFTRYPDV	471 IGEELSKMQL	436 NPENFDPARF	46 QLRSAPPGP
26 LLSVLA TVHV	436 NPENFDPARF	395 VPVTIPHATT	
23 LLLL SVLAT	392 SSFVPTIPH	252 NPVRTVFR E	HLA-B8 Octamers
4 SLSPNDPWPL	372 MG DQPNLPYV	496 NPNEPAKMNF	
336 STALQWLLL	365 GRDRLPCM GD	308 SHGGARLDL	Pos 12345678
456 LTSRVMIFS V	322 ATITDIFGAS	250 FPNPVRTVFR	159 QPRS RQVLEG
326 DIFGASQDTL	308 SHGGARLDL	159 QPRS RQVLEG	521 TLRESMEL
195 PLTVVAVAN V	292 MMDA FILSAE	88 RLGSCPIVVL	510 TIKPKSFK
	289 PRDMMDA FIL	513 PKSFKVNVT L	218 DPEFRELL

165 VLEGHVLSEA	279 HCESLRPGAA	499 EPAKMNFSYG	173 EARELVAL
38 RLLRQRRRQL	228 NEEFGRTVGA	473 EELSKMQLFL	515 SFKVNVTI
451 LINKDLTSRV	98 NGERAIHQAL	388 AMRFSSFVpv	414 IPKDTVVVF
388 AMRFSSFVpv	17 SIQQTLLLLL	330 ASQDTLSTAL	276 FLRHCESL
338 ALQWLLLLFT	9 DPWPLNPLSI	194 RPLTVVAVAN	473 EELSKMQL
509 LTIKPKSFKV	521 TLRESMELLD	171 LSEARELVAL	475 LSKMQLFL
502 KMNFSYGLTI	520 VTLRESMELL	63 AAAVGQAAHL	455 DLTSRVMI
334 TLSTALQWLL	402 ATTANTSVLG	15 PLSIQQTLL	444 RFLDKDGL
314 RLDLENVPAT	378 LPYVLAFLYE	4 SLSPNDPWPL	39 LLRQRRRQ
291 DMMMDAFLSA	290 RDMMMDAFLS	447 DKDGLINKDL	465 VGKRRCIG
263 QLNRFNSNFI	270 NFILDKFRLH	414 IPKDTVVVFVN	310 GGGARLDL
234 TVGAGSLVVD	265 NNRFSNFIID	378 LPYVLAFLYE	257 VFREFEQL
172 SEARELVAL	255 RTVFREFEQL	376 PNLPYVLAFL	170 VLSEAREL
63 AAAVGQAAHL	170 VLSEARELVA	336 STALQWLLLL	362 QVVGRDRL
21 TLLLLLLSVL	49 SAPPGPFAWP	335 LSTALQWLLL	40 LRQRRRQL
20 QTTLLELLSVD	32 TVHVGQRLLR	306 GDSHGGGARL	6 SPNDPWPL
477 KMQLFLFISI	31 ATVHVGQRLL	216 HDDPEFRELL	508 GLTIKPKS
450 GLINKDLTSR	515 SFKVNVTLRE	182 VRGSADGAFL	450 GLINKDLT
333 DTLSTALQWL	510 TIKPKSFKV	172 SEARELVAL	378 LPYVLAFL
248 QYFPNPVRTV	509 LTIKPKSFKV	157 TRQPRSRQVL	375 QPNLPYVL
86 QIRLGSCPIV	457 TSRVMIFSVG	68 QAAHLSFARL	353 QTRVQAEL
486 ILAHQCDFRA	407 TSVLGYHIPK	18 IQQTLLLLL	23 LLLLLSVL
481 FLFISILAHQ	362 QVVGDRDRLPC	16 LSIQQTLL	535 NLQAKETC
315 LDLENVPATI	346 FTRYPDVQTR	7 PNDPWPLNPL	512 KPKSFKV
192 DPRPLTVVAV	338 ALQWLLLLFT	527 ELDSAVQNL	498 NEPAKMNF
189 AFLDPRPLTV	337 TALQWLLLLF	466 GKRRCIGEEL	464 SVGKRRCI
171 LSEARELVAL	276 FLRHCESLRP	442 PARFLDKDGL	431 PLKWPNP
170 VLSEARELVA	217 DDPEFRELLS	430 DPLKWPNPEN	338 ALQWLLLL
106 ALVQQGSAFA	173 EARELVALLV	401 HATTANTSVL	299 SAEKKAAG
68 QAAHLSFARL	70 AHLSFARLAR	399 IPHATTANTS	17 SIQQTLL
22 TLLLELLSVA	48 RSAPPGPFAW	373 GDQPNLPYVL	9 DPWPLNPL
12 PLNPLSIQQT	33 VHVQQRLLRQ	334 TLSTALQWLL	384 FLYEAMRF
520 VTLRESMELL	23 LLLLELLSVLAT	326 DIFGASQDTL	364 VGRDRRLPC
408 SVLGYHIPKD	19 QQTLLLLLS	320 VPATITDIFG	271 FILDKFLR
376 PNLPYVLAFL	18 IQQTLLLLL	264 LNRNFSNFI	251 PNPVRTVF
351 DVQTRVQAEL	6 SPNDPWPLNP	255 RTVFREFEQL	190 FLDPRPLT
311 GGARLDENV	529 LDSAVQNLQA	244 MPWLQYFPNP	179 ALLVRGSA
226 SHNEEFGR	514 KSFKVNVTLR	231 FGRTVGAGSL	149 HSMMRNFF
198 VVAVANVMSA	502 KMNFSYGLTI	218 DPEFRELLSH	500 PAKMNFSY
180 LLVRGSADGA	479 QLFLFISILA	215 SHDDPEFREL	474 ELSKMQLF
29 VLATVHVGQR	477 KMQLFLFISI	187 DGAFLDPRPL	344 LLFTRYPD
18 IQQTLLLLL	463 FSVGKRRCIG	80 RYGDVFQIRL	337 TALQWLLL
15 PLSIQQTLL	444 RFLDKDGLIN	38 RLLRQRRRQL	282 SLRPGAAP
384 FLYEAMRFSS	434 WPNPENFDPA	31 ATVHVGQRLL	113 AFADRP
271 FILDKFLRHC	417 DTVVFVNQWS	17 SIQQTLLLLL	76 RLARRYGD
199 VAVANVMSAV	412 YHIPKDTVVF	6 SPNDPWPLNP	41 RQRRRQLR
179 ALLVRGSA	375 QPNLPYVLA	529 LDSAVQNLQA	486 ILAHQCDF
169 HVLSEAREL	328 FGASQDTLST	471 IGEELSKMQL	479 QLFLFISI
87 IRLGSCPIVV	307 DSHGGGARLD	441 DPARFLDKDG	445 FLDKDGLI
31 ATVHVGQRLL	282 SLRPGAAPRD	437 PENFDPARFL	377 NLPYVLA

519 NVTLRESMEL	257 VFREFEQLNR	423 NQWSVNHDP	336 STALQWLL
494 RANPNEPAKM	225 LSHNEEFGR	413 HIPKDTVVF	320 VPATITDI
479 QLFLFISILA	196 LTVVAVANVM	412 YHIPKDTVVF	286 GAAPRDMM
478 MQLFLFISIL	189 AFLDPRPLTV	390 RFSSFVPVTI	120 FASFRVVS
445 FLDKDGLINK	164 QVLEGHVLSE	360 LDQVVGDRDL	96 VLNGERA
418 TVVFVNQWSV	159 QPRSRQVLEG	351 DVQTRVQAL	78 ARRYYGDVF
410 LGYHIPKDTV	156 FTRQPRSRQV	338 ALQWLLLLFT	53 GPFAWPLI
372 MGDQPNLPYV	149 HSMMRNNFT	314 RLDLENVPAT	429 HDPLKWPN
342 LLLLFTRYPD	100 ERAIHQALVQ	313 ARLDLENVPA	387 EAMRFSSF
329 GASQDTLSTA	96 VLNGERAHQ	289 PRDMMDAFIL	312 GARLDLEN
308 SHGGGARLDL	82 GDVFQIRLGS	268 FSNFILDKFL	308 SHGGGARL
297 LSAEKKAAG	65 AVGQAAHLSF	238 GSLVDVMPWL	301 EKKAAGDS
296 FILSAEKKA	21 TTLLLLSVL	235 VGAGSLVDVM	298 LSAEKKA
282 SLRPGAAPRD	4 SLSPNDPWPL	181 LVRGSADGAF	288 APRDMMDA
215 SHDDPEFREL	2 GTSLSPNDPW	173 EARELVALLV	264 LNRNFSNF
164 QVLEGHVLSE	505 FSYGLTIKPK	170 VLSEARELVA	224 LLSHNEEF
156 FTRQPRSRQV	504 NFSYGLTIKP	162 SRQVLEGHVL	217 DDPEFREL
94 IVVLNGERA	494 RANPNEPAKM	148 AHSMRNNFT	192 DPRPLTVV
71 HLSFARLARR	480 LFLFISILAH	125 VVSGGRSMAF	164 QVLEGHVL
57 WPLIGNAAAV	473 EELSKMQLFL	98 NGERAIHQAL	140 HWKVQRRA
30 LATVHVGQRL	468 RRCIGEELSK	78 ARRYYGDVFQI	138 SEHWKVQR
16 LSIQQTTLLL	464. SVGKRRCIGE	65 AVGQAAHLSF	100 ERAIHQAL
511 IKPKSFKVNV	456 LTSRVMIFSV	53 GPFAWPLIGN	74 FARLARRY
469 RCIGEELSKM	449 DGLINKDLTS	47 LRSAPPGPFA	46 QLRSAPPG
398 TIPHATTANT	406 NTSVLGYHIP	26 LLSVLATVHV	11 WPLNPLSI
386 YEAMRFSSFV	393 SFVPVTIPHA	21 TTLLLLSVL	463 FSVGKRR
381 VLAFLYEAMR	391 FSSFVPVTIP	520 VTLRESMELL	452 INKDLTSR
373 GDQPNLPYVL	333 DTLSTALQWL	519 NVTLRESMEL	332 QDTLSTAL
363 VVGRDRRLPCM	332 QDTLSTALQW	511 IKPKSFKVNV	328 FGASQDTL
355 RVQAELDQVV	310 GGGARLDLEN	500 PAKMNFSYGL	270 NFILDKFL
354 TRVQAELDQV	291 DMMDAFILSA	492 DFRANPNEPA	240 LVDVMPWL
330 ASQDTLSTAL	266 RNFNSNFILEDK	478 MQLFLFISIL	184 GSADGAFL
238 GSLVDVMPWL	214 YSHDDPEFRE	475 LSKMQLFLFI	174 ARELVAL
177 LVALLVRGSA	157 TRQPRSRQVL	474 ELSKMQLFLF	90 GSCPIVVL
173 EARELVALLV	126 VSGGRSMAFG	462 1FSVGKRRCI	86 QIRLGSCP
102 AIHQALVQQG	87 IRLGSCPIVV	453 NKDLTSRVM	82 GDVFQIRL
96 VLNGERAHQ	55 FAWPLIGNAA	333 DTLSTALQWL	33 VHVGQRLL
75 ARLARRYGDV	52 PGPFAWPLIG	328 FGASQDTLST	32 TVHVGQRLL
55 FAWPLIGNAA	51 PPGPFAWPLI	274 DKFLRHCESL	20 QTLLLLL
50 APPGPF AWPL	40 LRQRRRQLRS	234 TVGAGSLVDV	18 IQQTTLLL
25 LLLSVLATVH	27 LSVLATVHVG	191 LDPRPLTVVA	529 LDSAVQNL
14 NPLSIQQTTL	5 LSPNDPWPLN	190 FLDPRPLTVV	522 LRESMELL
7 PNDPWPLNPL	455 DLTSRVMIFS	189 AFLDPRPLTV	513 PKSFKVNV
528 LLDSAVQNLQ	408 SVLGYHIPKD	168 GHVLSEAREL	502 KMNFSYGL
521 TLRESMELL	373 GDQPNLPYVL	147 AAHSMMRNFF	480 LFLFISIL
471 IGEELSKMQL	367 DRLPCMGDQP	139 EHWKVQRRAA	468 RRCIGEEL
466 GKRRRCIGEEL	330 ASQDTLSTAL	111 GSAFADRPAF	449 DGLINKDL
409 VLGYHIPDT	320 VPATITDIFG	110 QGSAFADRPA	446 LDKDGLIN

401 HATTANTSVL	268 FSNFILDKFL	106 ALVQQGSAFA	442 PARFLDKD
393 SFVPVTIPHA	250 FPNPVRTVFR	99 GERAIHQALV	439 NFDPARFL
380 YVLAFLYEA	248 QYFPNPVRTV	92 CPIVVLNGER	425 WSVNHDPL
369 LPCMGDQPNL	239 SLVDVMPWLQ	87 IRLGSCPPIV	412 YHIPKDTV
347 TRYPDVQTRV	192 DPRPLTVVAV	56 AWPLIGNAAA	403 TTANTSVL
344 LLFTRYPDVQ	172 SEARELVALL	30 LATVHVGQRL	371 CMGDQPNL
306 GDSHGGGARL	150 SMMRNFFTRQ	23 LLLLLSVLAT	335 LSTALQWL
292 MMDAFAILSAE	121 ASFRVVSGGR	11 WPLNPLSIQQ	321 PATITDIF
288 APRDMMDAFI	115 ADRPAFASFR	524 ESMELLDAS	300 AEKKAAGD
286 GAAPRDMMDA	111 GSAFADRPAF	523 RESMELLDAS	291 DMMDAFIL
272 ILDKFLRHCE	108 VQQGSAFADR	502 KMNFSYGLTI	273 LDKFLRHCE
255 RTVFREFEQL	12 PLNPLSIQQT	501 AKMNFSYGLT	266 RNFSNFI
239 SLVDVMPWLQ	531 SAVQNLQAKE	494 RANPNEPAKM	262 EQLNRNFS
235 VGAGSLVDVM	530 DSAVQNLQAK	469 RCIGEELSKM	233 RTVGAGSL
231 FGRTVGAGSL	524 ESMELLDAS	389 MRFSSFVPT	229 EEFGRTVG
224 LLSHNEEFGR	506 SYGLTIKPKS	355 RVQAELDQVV	220 EFRELLSH
182 VRGSADGAFL	484 ISILAHQCDF	318 ENVPATITDI	189 AFLDPRPL
168 GHVLSEAREL	432 LKWPNPENFD	304 AAGDSHGGGA	97 LNGERAIIH
162 SRQVLEGHVL	388 AMRFSSFVPV	291 DMMDAFILSA	77 LARRYGDV
131 SMAFGHYSEH	376 PNLPYVLAFL	287 AAPRDMMDAF	70 AHLSFARL
112 SAFADRPAFA	347 TRYPDVQTRV	278 RHCESLRPGA	65 AVGQAAHL
99 GERAIHQALV	318 ENVPATITDI	249 YFPNPVRTVF	52 PGPFAWPL
97 LNGERAIIHQ	317 LENVPATITD	228 NEEFGRTVGA	19 QQTTL
78 ARRYGDFVQI	298 LSAEKKAAGD	193 PRPLTVVAVA	16 LSIQQTTL
59 LIGNAAAVGQ	286 GAAPRDMMDA	161 RSRQVLEGHV	519 NVTLRESM
58 PLIGNAAAVG	281 ESLRPGAAAPR	114 FADRPAFASF	440 FDPARFLD
9 DPWPLNPLSI	269 SNFILDKFLR	112 SAFADRPAFA	392 SSFVPVTI
517 KVNVTLRESM	249 YFPNPVRTVF	86 QIRLGSCPPIV	280 CESLRPGA
500 PAKMNFSYGL	242 DVMPWLQYFP	76 RLARRYGDVF	274 DKFLRHCE
485 SILAHQCDFR	238 GSLVDVMPWL	75 ARLARRYGDV	126 VSGGRSMA
403 TTANTSVLGY	235 VGAGSLVDVM	61 GNAAAVGQAA	122 SFRVVSGG
390 RFSSFVPVTI	204 VMSAVCFGCR	60 IGNAAAVGQAA	84 VFQIRLGS
360 LDQVVGRDRL	162 SRQVLEGHVL	46 QLRSAPPGPF	44 RRQLRSAP
341 WLLLFLTRYP	161 RSRQVLEGHV	41 RQRRRQLRSA	37 QRLLRQRR
335 LSTALQWL	130 RSMAFGHYSE	532 AVQNLQAKET	34 HVGQRL
323 TITDIFGASQ	117 RPAFASFRVV	517 KVNVTLRESM	527 ELLDSAVQ
316 DLENVPATIT	80 RYGDVFQIRL	486 ILAHQCDFRA	499 EPAKMNF
304 AAGDSHGGGA	79 RRYGDVFQIR	477 KMQLFLFISI	496 NPNEPAKM
276 FLRHCESLRP	64 AAVGQAAHLS	456 LTSRVMIFSV	490 QCDFRANP
274 DKFLRHCESL	53 GPFAWPLIGN	454 KDLTSRVMIF	476 SKMQLFLF
264 LNRNFNSNFI	39 LLRQRRQQLR	452 INKDLTSRVM	438 ENFDPARF
216 HDDPEFRELL	11 WPLNPLSIQQ	451 LINKDLTSRV	409 VLGYHIPK
185 SADGAFLDPR	3 TSLSPNDPWP	448 KDGLINKDLT	386 YEAMRFSS
176 ELVALLVRGS	501 AKMNFSYGLT	443 ARFLDKDGLI	359 ELDQVVGR
157 TRQPRSRQVL	499 EPAKMNFSYG	411 GYHIPKDTVV	351 DVQTRVQA
142 KVQRRAAHSM	487 LAHQCDFRAN	405 ANTSVLGYHI	346 FTRYPDVQ
134 FGHYSEHWKV	474 ELSKMQLFLF	400 PHATTANTS	269 SNFILDKF
119 AFASFRVVSG	469 RCIGEELSKM	398 TIPHATTANT	261 FEQLNRNF

101 RAIHQALVQQ	459 RVMIFSVGKR	393 SFVPVTIPHA	255 RTVFREFE
76 RLARRYGDVF	443 ARFLDKDGLI	386 YEAMRFSSFV	254 VRTVFREF
39 LLRQRRRQLR	440 FDPARFLDKD	385 LYEA MRFSSF	239 SLVDVMPW
532 AVQNLQAKET	438 ENFDPARFLD	380 YVLAFLYEA M	223 ELLSHNEE
525 SME LLD SAVQ	384 FLYEA MRFSS	374 DQPNL PYVLA	211 GCRYSHDD
524 ESMELLD SAV	381 VLAFLYEA MR	372 MG DQPNL PYV	209 CFG CRYSH
474 ELSKMQLFLF	370 PCMGD QPNLP	363 VVGRDRLPCM	176 ELV ALLVR
459 RVMIFSVGKR	352 VQTRVQAELD	347 TRY PDVQTRV	171 LSEARELV
443 ARFLDKDGLI	334 TLSTALQWLL	345 LFTRY PDVQT	157 TRQPRSRQ
442 PARFLDKDGL	309 HGGGARLDLE	337 TALQWLLL LF	154 NFFTRQPR
423 NQWSVNH DPL	295 AFILSAEKKA	329 GASQDTLSTA	142 KVQRRAAH
421 FVNQWSVNH D	262 EQLNRNFSNF	319 NVPATITDIF	141 WKVQRRAAH
411 GYHIPKDTVV	252 NPVRTV FREF	295 AFILSAEKKA	127 SGGRSMAF
400 PHATTANTSV	246 WLQYFPNPVR	286 GAAPRDMMDA	75 ARLARRYG
394 FVPVTIPHAT	244 MPWLQYFPNP	283 LRPGAAPRDM	72 LSFARLAR
337 TALQWLLL LF	232 GRTVGAGSLV	267 NFSNFI LDKF	36 GQRLLRQR
318 ENVPATITDI	226 SHNEEF GRTV	262 EQLNRNFSNF	4 SLS PNDPW
313 ARLDLEN VPA	188 GAFLDPRPLT	248 QYFPNPVRTV	504 NFSYGLTI
196 LTVVAVANVM	169 HVLSEARELV	247 LQYFPNPVRT	481 FLFISILA
188 GAFLDPRPLT	134 FGHYSEHWKV	201 VANVMSAVCF	477 KMQLFLFI
150 SMMRNFFTRQ	122 SFRVVSGGRS	199 VAVANVMSAV	466 GKRR CIGE
117 RPAFASFRVV	89 LGSCP IVVVLN	198 VVAVANVMSA	457 TSRVMIFS
85 FQIRLGSCPI	76 RLARRYGDVF	195 PLTVVAVANV	407 TSVLG YHI
80 RYGDVFQIRL	73 SFARLARRYG	188 GAFLDPRPLT	399 IPHATTAN
60 IGNAAAVGQA	69 AAHLSFARLA	177 LVALLVRGSA	395 VPVTIPHA
28 SVLATVHVGQ	68 QAAHLSFARL	165 VLEGHVLSEA	381 VLAFLYEA
531 SAVQNLQAKE	58 PLIGNAAVG	156 FTRQPRSRQV	366 RDRLPCM G
523 RESMELLD SA	29 VLATVHVGQR	146 RAAHSMMRNF	349 YPDVQTRV
513 PKSFKVNVTL	22 TLLLLS VLA	143 VQRRAAH SMM	342 LLLL FTRY
508 GLTIKPKSFK	15 PLSIQQTLL	124 RVVSGGRSMA	341 WLLLLFTR
475 LSKMQLFLFI	8 NDPWPLNPLS	94 IVVLNGERAI	339 LQWLLL LF
473 EELSKMQLFL	527 EL LDSAVQNL	69 AAHLSFARLA	317 LENVPATI
462 IF SVGKRR CI	518 VNVTLRESME	66 VGQAAHLSFA	314 RLDLEN VP
453 NKDLTSRVMI	512 KPKSFKVNV	55 FAWPLIGNAA	297 ILSAEKKA
447 DKDGLINKDL	507 YGLTIKPKSF	22 TLLLLS VLA	272 ILDKFLRH
426 SVNH DPLKWP	495 ANPNEPAKMN	20 QTTL LLLLSV	250 FPNPVRTV
405 ANTSVLGYHI	488 AHQCDFRANP	509 LTIKPKSFKV	246 WLQYFPNP
397 VTI PHATTAN	485 SILAHQCDFR	484 ISILAHQCDF	244 MPWLQYFP
389 MRFSSFVPVT	481 FLFISILA HQ	409 VLGYHIPKDT	243 VMPWLQYF
371 CMGDQPNLPY	476 SKMQLFLFIS	396 PVTIPHATTA	231 FGRTVGAG
368 RLPCMGDQPN	467 KRRCIGEELS	394 FVPVTIPHAT	195 PLTVVAVA
357 QAELDQVVGR	460 VMIFSVGKRR	343 LLLFTRYPDV	165 VLEGHVL S
346 FTRYPDVQTR	458 SRVMIFSVGK	316 DLENVPATIT	156 FTRQPRSR
328 FGASQDTLST	448 KDGLINKDLT	315 LDLENVPATI	143 VQRRAHS
303 KAAGD SHGGG	446 LDKDGLINKD	311 GGARLDLEN	128 GGRSMAFG
268 FSNFILDKFL	426 SVNHDPLKWP	296 FILSAEKKA A	99 GERAIHQ A
246 WLQYFPNPVR	424 QWSVNH DPLK	279 HCESLRPGAA	92 CPIVVLNG
245 PWLQYFPNPV	422 VNQWSVNH D	263 QLN RNF SNFI	87 IRLGSCPI

232 GRTVGAGSLV	421 FVNQWSVNHD	259 REFEQLNRNF	71 HLSFARLA
200 AVANVMSAVC	419 VVFVNQWSVN	245 PWLQYFPNPV	67 GQAAHLSF
187 DGAFLDPRPL	414 IPKDTVVFVN	225 LSHNEEFGR	29 VLATVHVG
161 RSRQVLEGHV	409 VLGYHIPKDT	222 RELLSHNEEF	26 LLSVLATV
98 NGERAIHQAL	405 ANTSVLGYHI	212 CRYSHDDPEF	24 LLLLSQLA
83 DVFQIRLGSC	389 MRFSSFVPVT	196 LTVVAVANVM	22 TLLLLSV
69 AAHLSFARLA	386 YEAMRFSSFV	169 HVLSEARELV	531 SAVQNLQA
49 SAPPGPFAWP	380 YVLAFLYEA	142 KVQRRAAHSM	528 LLDSAVQN
46 QLRSAPPGPF	374 DQPNLPYVLA	116 DRPAFASFRV	509 LTIKPKSF
41 RQRRRQLRSA	364 VGRDRLPCM	105 QALVQQGS	492 DFRANPNE
512 KPKSFKVNV	361 DQVVGRDRLP	104 HQALVQQGSA	485 SILAHQCD
483 FISILAHQCD	358 AEILDQVVGRD	97 LNGERAIHQ	470 CIGEELSK
480 LFLFISILAH	356 VQAELDQVVG	85 FOIRLGSCPI	467 KRRCIGEE
470 CIGEELSKMQ	344 LLFTRYPDVQ	54 PFAWPLIGNA	456 LTSRVMIF
461 MIFSVGKRR	342 LLLLFTTRYPD	24 LLLLSQLATV	441 DPARFLDK
460 VMIFSVGKRR	327 IFGASQDTLS	12 PLNPLSIQQT	436 NPENFDPA
446 LDKDGLINKD	313 ARLDLENVPA	507 YGLTIKPKSF	434 WPNPENFD
404 TANTSVLGYH	304 AAGDSHGGGA	479 QLFLFISILA	433 KWPNPENF
395 VPVTIPHATT	300 AEKKAAGDSH	472 GEELSKMQLF	430 DPLKWPNP
377 NLPYVLAFLY	294 DAFILSAEKK	431 PLKWPNPENF	388 AMRFSSFV
358 AEILDQVVGRD	284 RPGAAPRDMM	418 TVFVNQWSV	369 LPCMGDQP
339 LQWLLLLFTR	275 KFLRHCESLR	410 LGYHIPKDT	368 RLPCMGDQ
322 ATITDIFGAS	267 NFSNFILDKF	382 LAFLYEAMRF	343 LLLFTTRYP
321 PATITDIFGA	261 FEQLNRFNSN	379 PYVLAFLYEA	334 TLSTALQW
298 LSAEKKAAGD	256 TVFREFEQLN	362 QVVGRDRLPC	316 DLENVPAT
295 AFILSAEKK	237 AGSLVDVMPW	354 TRVQAELDQV	290 RDMMDAFI
243 VMPWLQYFPN	229 EEFGRTVGAG	325 TDIFGASQDT	289 PRDMMDAF
223 ELLSHNEEF	208 VCFGCRYSHD	321 PATITDIFGA	284 RPGAAPRD
204 VMSAVCFGCR	207 AVCFGCRYSH	297 ILSAEKKAA	265 NRNFSNFI
181 LVRGSADGAF	206 SAVCFGCRYS	241 DVMPWLQYF	263 QLNRFNSN
120 FASFRVVSGG	202 ANVMSAVCFG	237 AGSLVDVMPW	253 PVRTVFRE
116 DRPAFASFRV	200 AVANVMSAVC	233 RTVGAGSLVD	252 NPVRTVFR
114 FADRPFAFASF	198 VVAVANVMSA	232 GRTVGAGSLV	214 YSHDDPEF
95 VVLNGERAIH	197 TVVAVANVMS	226 SHNEEFRTV	206 SAVCFGCR
93 PIVVNLNGERA	195 PLTVVAVANV	180 LLVRGSADGA	203 NVMSAVCF
66 VGQAAHLSFA	193 PRPLTVVAVA	138 SEHWKVQRRA	201 VANVMSAV
65 AVGQAAHLSF	183 RGSADGAFLD	134 FGHYSEHWKV	194 RPLTVVAV
64 AAVGQAAHLS	182 VRGSADGAFL	123 FRVVSGGRSM	188 GAFLDPRP
62 NAAAVGQAAH	179 ALLVRGSADG	119 AFASFRVVSG	185 SADGAFLD

56 AWPLIGNAAA	178 VALLVRGSAD	115 ADRPAFASFR	183 RGSADGAF
510 TIKPKSFKVN	176 ELVALLVRGS	93 PIVVLNGERA	181 LVRGSADG
455 DLTSRVMIFS	163 RQVLEGHVL	70 AHLSFARLAR	180 LLVVRGSAD
412 YHIPKDTVVF	158 RQPRSQRQVLE	13 LNPLSIQQTT	178 VALLVRGS
379 PYVLAFLYEAA	155 FFTRQPRSRQ	439 NFDPARFLDK	161 RSRQVLEG
349 YPDVQTRVQA	148 AHSMMRNFFT	402 ATTANTSVLG	151 MMRNFFTR
283 LRPGAAPRDM	147 AAHSMMRNFF	229 EEFGRTVGAG	148 AHSMMRNF
278 RHCESLRPGA	143 VQRRAAHSM	200 AVANVMSAVC	144 QRRAAHSM
247 LQYFPNPVRT	138 SEHWKVQRR	186 ADGAFLDPRP	117 RPAFASFR
207 AVCFGCRYSH	131 SMAFGHYSEH	174 ARELVALLVR	116 DRPAFASF
201 VANVMSAVCF	127 SGGRSMAFGH	126 VSGGRSMAFG	115 ADRPAFAS
191 LDPRPLTVVA	125 VVSGGRSMAF	118 PAFASFRVVS	112 SAFADRPA
178 VALLVRGSAD	124 RVVSGGRSMA	100 ERAIHQALVQ	107 LVQQGSAF
175 RELVALLVRG	123 FRVVSGGRSM	89 LGSCPIVVLN	106 ALVQQGSA
151 MMRNFFTRQP	120 FASFRVVS	77 LARRYGDVFQ	88 RLGSPIV
125 VVSGGRSMAF	119 AFASFRVVS	43 RRRQLRSAPP	80 RYGDVFQI
124 RVVSGGRSMA	118 PAFASFRVVS	521 TLRESMELLD	58 PLIGNAAA
104 HQALVQQGSA	112 SAFADRPAFA	514 KSFKVNTLR	57 WPLIGNAA
91 SCPIVVLNGE	106 ALVQQGSAFA	488 AHQCDFRANP	51 PPGPFAWP
90 GSCPIVVLNG	102 AIHQALVQQG	457 TSRVMIFS	50 APPGPFAW
89 LGSCPIVVNL	99 GERAIHQALV	415 PKDTVVFVNQ	49 SAPPGPFA
77 LARRYGDVFQ	95 VVLNGERAIIH	403 TTANTSVLGY	48 RSAPPGPFF
61 GNAAAVGQAA	91 SCPIVVLNGE	397 VTIPHATTAN	43 RRRQLRSA
51 PPGPFAWPLI	88 RLGSPIVVL	391 FSFVPTIP	42 QRRRQLRS
34 HVGQRLLRQR	84 VFQIRLGSCP	371 CMGDQPNLPY	38 RLLRQRRR
33 VHVGQRLLRQ	78 ARRYGDVFQI	356 VQAELDQVVG	25 LLLSVLAT
13 LNPLSIQQTT	74 FARLARRYGD	353 QTRVQAELDQ	15 PLSIQQTT
529 LDSAVQNLQA	56 AWPLIGNAAA	327 IFGASQDTLS	14 NPLSIQQTT
516 FKVNVTLRES	50 APPGPFAWPL	322 ATIDIFGAS	12 PLNPLSIQ
505 FSYGLTIKPK	38 RLLRQRRQL	310 GGGARLDLEN	483 FISILAHQ
501 AKMNFSYGLT	35 VGQRLLRQRR	305 AGDSHGGGAR	413 HIPKDTVV
487 LAHQCDFRAN	28 SVLATVHVGQ	303 KAAGDSHGGG	401 HATTANTS
476 SKMQLFLFIS	25 LLLSVLATVH	282 SLRPGAAPRD	382 LAFLYEAM
464 SVGKRCIGE	533 VQNLQAKETC	280 CESLRPGAAP	357 QAEQDQVV
454 KDLTSRVMIF	532 AVQNLQAKET	276 FLRHCESLRP	329 GASQDTLS
440 FDPARFLDKD	517 KVNVTLRESM	272 ILDKFLRHCE	296 FILSAEKK
437 PENFDPARFL	516 FKVNVTLRES	257 VFREFEQLNR	236 GAGSLVVDV
434 WPNPENFDPA	513 PKSFKVNVTL	253 PVRTVFREFE	199 VAVANVMS
402 ATTANTSVLG	508 GLTIKPKSFK	213 RYSHDDPEFR	114 FADRPAFA
382 LAFLYEAMRF	493 FRANPNEPAK	204 VMSAVCFGCR	105 QALVQQGS
375 QPNLPYVLAF	492 DFRANPNEPA	202 ANVMSAVCFG	93 PIVVLNGE
362 QVVGRDRRLPC	486 ILAHQCDFRA	185 SADGAFLDPR	69 AAHLSFAR
359 ELDQVVGDR	483 FISILAHQCD	184 GSADGAFLDP	63 AAAVGQAA
356 VQAELDQVVG	470 CIGEELSKMQ	183 RGSADGAFLD	55 FAWPLIGN
345 LFTRYPDVQT	466 GKRRCIGEEL	136 HYSEHWKVQR	30 LATVHVGG

289 PRDMMDAFIL	465 VGKRRCIGEE	113 AFADRPASFAS	524 ESMELLDS
287 AAPRDMMDAF	462 IFSVGKRRCI	108 VQQGSAFADR	494 RANPNEPA
242 DVMPWLQYFP	454 KDLTSRVMIF	90 GSCPIVVLNG	487 LAHQCDFR
240 LVDVMPWLQY	452 INKDLTSRVM	79 RRYGDVFQIR	461 MIFSVGKR
236 GAGSLVDVMP	450 GLINKDLTSR	64 AAVGQAAHLS	451 LINKDLTS
233 RTVGAGSLVD	433 KWPNPENFDP	62 NAAAVGQAAH	404 TANTSVLG
193 PRPLTVVAVA	431 PLKWPNPENF	58 PLIGNAAAVG	398 TIPHATTA
159 QPRSQRQVLEG	430 DPLKWPNPEN	48 RSAPPGPFAW	326 DIFGASQD
147 AAHSMMRNFF	427 VNHDPLKWPN	42 QRRRQLRSAP	323 TITDIFGA
132 MAFGHYSEHW	420 VFVNQWVSNH	33 VHVGQRLLRQ	304 AAGDSHGG
123 FRVVSGGRSM	416 KDTVVVFVNQW	515 SFKVNVTLRE	303 KAAGDSHG
107 LVQQGSAFAD	413 HIPKDTVVVF	510 TIKPKSFKVN	294 DAFLSAE
105 QALVQQGSAF	411 GYHIPKDTVV	505 FSYGLTIKPK	287 AAPRDMMMD
74 FARLARRYGD	401 HATTANTSVL	504 NFSYGLTIKPK	226 SHNEEFGR
54 PFAWPLIGNA	400 PHATTANTS	493 FRANPNEPAK	147 AAHSMMRN
53 GPFAPLIGN	395 VPVTIPHATT	480 LFLFISILAH	146 RAAHSMMR
47 LRSAPPGPFA	394 FVPVTIPHAT	468 RRCIGEELSK	132 MAFGHYSE
27 LSVLATVHVG	387 EAMRFSSFVP	467 KRRCIGEELS	118 PAFASFRV
530 DSAVQNLQAK	383 AFLYEAMRFS	463 FSVGKRCIG	102 AIHQALVQ
522 LRESMELLDS	368 RLPPCMGDQPN	459 RVMIFSVGKR	101 RAIHQALV
514 KSFKVNVTLR	363 VVGRDRLPCM	444 RFLDKDGLIN	68 QAAHLSFA
465 VGKRRCIGEE	360 LDQVVGRDRL	428 NHDPLKWPNP	64 AAVGQAAH
452 INKDLTSRVM	355 RVQAELDQVV	424 QWSVNHDPLK	62 NAAAVGQA
432 LKWPNPENFD	350 PDVQTRVQAE	408 SVLGYHIPKD	59 LIGNAAAV
431 PLKWPNPENF	348 RYPDVQTRVQ	387 EAMRFSSFVP	525 SMELLDSDA
419 VVFVNQWVSN	343 LLLFTRYPDV	383 AFLYEAMRFS	506 SYGLTIKPK
414 IPKDTVVVFVN	341 WLLLFLTRYP	370 PCMGDQPNLP	471 IGEELSKM
396 PVTIPHATTA	326 DIFGASQDTL	366 RDRLPCMGDQ	356 VQAELDQV
324 ITDIFGASQD	323 TITDIFGASQ	358 AELDQVVGRD	227 HNEEFGR
312 GARLDLENVP	312 GARLDLENVP	357 QAELDQVVGR	167 EGHVLSEA
309 HGGGARLDLE	306 GDSHGGGARL	348 RYPDVQTRVQ	162 SRQVLEGH
294 DAFLSAEKK	303 KAAGDSHGGG	346 FTRYPDVQTR	136 HYSEHWKV
277 LRHCESLRPG	297 ILSAEKKAAAG	331 SQDTLSTALQ	533 VQNLQAKE
267 NFSNFIILDKF	296 FILSAEKKA	312 GARLDLENVP	484 ISILAHQC
266 RNFSNFIILDK	288 APRDMMDAFI	309 HGGGARLDLE	472 GEELSKMQ
250 FPNPVRTVFR	287 AAPRDMMDAF	302 KKAAGDSHGG	462 IFSVGKRR
237 AGSLVDVMPW	285 PGAAPRDMMMD	300 AEKKAAGDSH	458 SRVMIFSV
225 LSHNEEFGR	283 LRPGAAPRDM	292 MMDAFLSAE	435 PNPNENFDP
206 SAVCFGCRYS	280 CESLRPGAAP	290 RDMMDAFILS	426 SVNHDPLK
203 NVMSAVCFG	278 RHCESLRPGA	281 ESLRPGAAPR	419 VVFVNQWS
202 ANVMSAVCFG	271 FILDKFLRHC	270 NFILDKFLRH	408 SVLGYHIP
197 TVVAVANVMS	264 LNRNFSNFI	266 RNFSNFIILDK	394 FVPVTIPH
174 ARELVALVLR	263 QLNRFNSNFI	260 EFEQLNRNFS	393 SFVPVTIP
148 AHSMMRNFFT	259 REFEQLNRNF	242 DVMPWLQYFP	331 SQDTLSTA

146 RAAHSMMRNF	254 VRTVFRFEQ	240 LVDVMPWLQY	318 ENVPATIT
138 SEHWKVQRRA	253 PVRTVFRFE	236 GAGSLVDVMP	315 LDLENVPA
113 AFADRPAFAS	251 PNPVRTVFR	230 EFGRTVGAGS	281 ESLRPGAA
81 YGDVFQIRLG	243 VMPWLQYFPN	227 HNEEFGRTVG	278 RHCESLRP
70 AHLSFARLAR	241 VDVMPLQYF	220 EFRELLSHNE	260 EFEQLNRN
507 YGLTIKPKSF	236 GAGSLVDVMP	211 GCRYSHDDPE	259 REFEQLNR
506 SYGLTIKPKS	231 FGRTVGAGSL	207 AVCFGCRYSH	238 GSLVDVMP
503 MNFSYGLTIK	230 EFGRTVGAGS	197 TVVAVANVMS	232 GRTVGAGS
493 FRANPNEPAK	224 LLSHNEEFGR	179 ALLVRGSADG	230 EFGRTVGA
482 LFISILAHQC	223 ELLSHNEEFG	176 ELVALLVRGS	221 FRELLSHN
458 SRVMIFSVGK	222 RELLSHNEEF	175 RELVALLVRG	215 SHDDPEFR
448 KDGLINKDLT	210 FGCRYSHDDP	164 QVLEGHVLSE	198 VVAVANVM
416 KDTVVVFVNQW	201 VANVMSAVCF	163 RQVLEGHVL	172 SEARELVA
406 NTSQLGYHIP	199 VAVANVMSAV	158 RQPRSRQVLE	168 GHVLSEAR
399 IPHATTANTS	191 LDPRPLTVVA	151 MMNRNFFTTRQP	150 SMMRNFFT
374 DQPNLPYVLA	186 ADGAFLDPRP	150 SMMRNFFTTRQ	139 EHWKVQRRA
353 QTRVQAELDQ	181 LVRGSADGAF	145 RRAAHSMRNR	134 FGHYSEHW
325 TDIFGASQDT	180 LLVRGSADGA	144 QRRAAHSMRNR	131 SMAFGHYS
317 LENVPATITD	177 LVALLVRGSA	140 HWKVQRRAAH	123 FRVVSGGR
302 KKAAGDSSHGG	152 MRNFFTTRQPR	133 AFGHYSEHWK	104 HQALVQQG
299 SAEKKAAGDS	144 QRRAAHSMRNR	130 RSMAFGHYSE	94 IVVLNGER
293 MDAFILSAEK	140 HWKVQRRAAH	128 GGRSMAFGHY	91 SCPIVVNL
256 TVFRFEQLN	139 EHWKVQRRAAH	120 FASFRVVSGG	73 SFARLARR
241 VDVMPLQYF	135 GHYSEHWKVQ	102 AIHQALVQQG	28 SVLATVHV
229 EEFGRTVGAG	133 AFGHYSEHWK	101 RAIHQALVQQ	2 GTSLSPND
228 NEEFGRTVGA	132 MAFGHYSEHW	82 GDVFQIRLGS	530 DSAVQNLQ
194 RPLTVVAVAN	129 GRSMAGHYS	74 FARLARRYGD	526 MELLDASAV
184 GSADGAFLDP	113 AFADRPAFAS	71 HLSFARLARR	520 VTLRESME
143 VQRRAAHSM	105 QALVQQGSF	67 GQAAHLSFAR	518 VNVTLRES
137 YSEHWKVQRRA	93 PIVVNLNGERA	59 LIGNAAAVGQ	517 KVNVTLRE
126 VSGGRSMAFG	92 CPIVVLNGER	49 SAPPGPFAWP	516 FKVNVTLR
108 VQQGSAFADR	85 FQIRLGSCPI	44 RRQLRSAPPG	511 IKPKSFKV
48 RSAPPGPFAW	75 ARLARRYGDV	39 LLRQRRRQLR	505 FSYGLTIK
32 TVHVGQRLLR	71 HLSFARLARR	32 TVHVGQRLLR	493 FRANPNEP
6 SPNDPWPLNP	66 VGQAAHLSFA	28 SVLATVHVGQ	489 HQCDFRAN
2 GTSLSPNDPW	63 AAAVGQAAHL	2 GTSLSPNDPW	460 VMIFSVGK
533 VQNLQAKETC	61 GNAAAVGQAA	530 DSAVQNLQAK	453 NKDLTSRV
526 MELLDASAVQN	60 IGNAAAVGQA	526 MELLDASAVQN	448 KDGLINKD

491 CDFRANPNEP	47 LRSAPPGPFA	525 SMELLD SAVQ	443 ARFLDKDG
488 AHQCDFRANP	46 QLRSAPPGPF	522 LRESMELLDS	427 VNHDPLKW
484 ISILAHQCDF	42 QRRRQLRSAP	506 SYGLTIKPKS	424 QWSVNHDP
449 DGLINKDLTS	37 QRLLRQRQQRQ	497 PNEPAKMNF	422 VNQWSVNH
444 RFLDKDGLIN	30 LATVHVGQRL	495 ANPNEPAKM	421 FVNQWSVN
430 DPLKWPNPEN	26 LLSVLATVHV	490 QCDFRANPNE	420 VFVNQWSV
391 FSSFVVPVTIP	24 LLLSVLATV	487 LAHQCDFRAN	417 DTVVFVNQ
378 LPYVLAFLYE		485 SILAHQCDFR	416 KDTVVFVN
331 SQDTLSTALQ	HLA-A26 Nonamers	483 FISILAHQCD	411 GYHIPKDT
319 NVPATITDIF		464 SVGKRCIGE	406 NTSQLGYH
310 GGGARLDLEN	Pos 123456789	458 SRVMIFSVGK	397 VTIPHATT
284 RPGAAPRDMM	242 DVMPWLQYF	449 DGLINKDLTS	391 FSSFVVPVT
279 HCESLRPGAA	455 DLTSRVMIF	445 FLDKDGLINK	383 AFLYEAMR
258 FREFEQLNRN	470 CIGEELSKM	438 ENFDPARFLD	379 PYVLAFLY
257 VFREFEQLNR	223 ELLSHNEEF	435 PNPNENFDPAR	373 GDQPNLPY
222 RELLSHNEEF	260 EFEQLNRNF	432 LKWPNPENFD	365 GRDRLPCM
218 DPEFRELLSH	256 TVFREFEQL	425 WSVNHDPLKW	363 VVGRDRLP
212 CRYSHDDPEF	253 PVRTVVFREF	420 VFVNQWSVNH	361 DQVVGRDR
208 VCFGCRYSHD	528 LLDSAVQNL	416 KDTVVFVNQW	360 LDQVVGRD
136 HYSEHWKVQR	341 WLLLLFTRY	406 NTSQLGYHIP	352 VQTRVQAE
130 RSMAFGHYSE	263 QLNRRNSNF	392 SSFVPTIPH	340 QWLLLLFT
121 ASFRVVS GGR	521 TLRESMELL	381 VLAFLYEAMR	327 IFGASQDT
118 PAFASFRVVS	479 QLFLFISIL	368 RLPCMGDQPN	324 ITDIFGAS
115 ADRPAFASFR	474 ELSKMQLFL	364 VGRDRLPCM	311 GGARLDLE
111 GSAFADRPAF	473 EELSKMQLF	359 ELDQVVGRDR	309 HGGARLD
110 QGSAFADRPA	413 HIPKDTVVF	350 PDVQTRVQAE	306 GDSHGGGA
92 CPIVVLNGER	381 VLAFLYEAM	342 LLLLFTTRYPD	295 AFILSAEK
73 SFARLARRYG	338 ALQWLLLLF	340 QWLLLLFTTRY	279 HCESLRPG
67 GQAAHLSFAR	377 NLPYVLAFL	332 QDTLSTALQW	268 FSNFILDK
45 RQLRSAPPGP	351 DVQTRVQAE	324 ITDIFGASQD	258 FREFEQLN
19 QQTLLL	239 SLVDVMPWL	307 DSHGGARLD	241 VDVMWPLQ
496 NPNEPAKMNF	173 EARELVAL	301 EKKAAGDSHG	237 AGSLVDVM
492 DFRANPNEPA	106 ALVQQGSAF	298 LSAEKKAAGD	235 VGAGSLVD
468 RRCIGEELSK	22 TLLLLLSVL	293 MDAFILSAEK	222 RELLSHNE
463 FSVGKRCIG	417 DTVVFVNQW	285 PGAAPRDMM	216 HDDPEFRE
439 NFDPARFLDK	359 ELDQVVGRD	246 WLQYFPNPVR	210 FGCRYSHD
428 NHDPPLKWPNP	334 TLSTALQWL	224 LLSHNEEFGR	208 VCFGCRYS
425 WSVNHDPLKW	326 DIFGASQDT	223 ELLSHNEEFG	205 MSAVCFGC
420 VFVNQWSVNH	220 EFRELLSHN	217 DDPEFRELLS	204 VMSAVCFG
417 DTVVFVNQWS	176 ELVALLVRG	208 VCFGCRYSHD	196 LTVVAVAN
392 SSFVPTIPH	520 VTLRESMEL	167 EGHVLSEARE	193 PRPLTVVA
385 LYEAAMRFSSF	508 GLTIKPKSF	166 LEGHVLSEAR	182 VRGSADGA
383 AFLYEAMRFS	485 SILAHQCD	160 PRSRQVLEGH	177 LVALLVRG
367 DRLPCMGDQP	336 STALQWLLL	153 RNFFTRQPRS	175 RELVALLV
320 VPATITDIFG	169 HVLSEAREL	152 MRNFFTRQPR	169 HVLSEARE
305 AGDSHGGGAR	124 RVVSGGRSM	149 HSMMRNFFTR	163 RQVLEGHV
300 AEKKAAGDSH	83 DVFQIRLGS	132 MAFGHYSEHW	155 FFTRQPRS
280 CESLRPGAAP	31 ATVHVGQRL	129 GRSMAFGHYS	135 GHYSEHWK
275 KFLRHCESLR	499 EPAKMNF SY	122 SFRVVSGGRS	129 GRSMAFGH

270 NFI	402 ATT	121 ASF	125 VV
269 SNF	73 SF	103 IHQ	111 GSA
261 FEQ	17 SIQ	96 VLNG	108 VQQ
259 REFE	527 ELL	95 VLNG	103 IHQ
221 FRELL	383 AFL	73 SF	95 VLNG
214 YSH	333 DTL	52 PG	85 FQIR
186 ADG	307 DSH	45 RQL	81 YGD
166 LEH	197 TVV	40 LRQ	66 VGQAA
154 NFF	115 ADR	36 GQR	61 GNAAAV
149 HSMM	39 LLR	29 VLAT	60 IGN
139 EH	32 TVH	27 LSV	56 AWPL
133 AFG	438 ENF	25 LLS	35 VGQR
127 SGGR	394 FVP	19 QQT	27 LSV
103 IHQ	386 YEAM	534 QNL	21 TT
79 RRY	376 PNLP	531 SAV	13 LNPL
72 LSF	322 ATID	528 LLD	10 PWPL
40 LRQ	271 FIL	508 GLT	HLA-B8 Nonamers
5 LSP	230 EFG	503 MNF	
3 TSL	217 DDPE	498 NEPA	
534 QNL	200 AVAN	489 HQCD	Pos 1
515 SFK	177 LVALL	481 FLFIS	2 3 4 5 6 7 8 9
498 NEPA	102 AIHQ	476 SKMQL	39 LLRQ
489 HQCD	15 PLSI	470 CIGEEL	173 EARELV
427 VNHD	481 FLFIS	455 DLTSR	521 TLRESMELL
422 VNQW	475 LSKMQL	450 GLINKDL	510 TIKPKSF
387 EAMRF	451 LINKDL	440 FDPA	508 GLTIKPKSF
365 GRDRL	404 TANTS	433 KWP	455 DLTSRVMIF
364 VGRDRL	374 DQPNLP	429 HDPL	159 QPRSRQVLE
350 PDVQ	323 TITDIF	427 VNHDPL	465 VGKRCIGE
340 QWL	288 APRDMM	421 FVNQW	414 IPKDTVV
327 IFG	216 HDDPE	419 VVFVNQ	288 APRDMM
273 LDK	196 LTVVAV	407 TSVLGY	479 QLFLFISIL
254 VRTV	147 AAHS	384 FLYEAM	474 ELSKMQLFL
252 NPVRTV	34 HVGQ	367 DRLPC	473 EELSKMQLF
249 YFPN	21 TTL	365 GRDRL	431 PLKWP
244 MPWL	517 KVNV	344 LLFTRY	239 SLVDVMPWL
219 PEFRELL	510 TIKPKSF	341 WLLL	99 GERAIHQAL
217 DDPEFRELL	482 LFISILA	323 TITDIF	528 LLD
205 MSAVCF	447 DKDGLINKD	317 LENVPATITD	512 KPKSF
163 RQV	380 YVLAFL	299 SAEKKAAGDS	467 KRRCIGEEL
160 PRSRQV	361 DQVVGR	277 LRHCESLRPG	463 FSVGKRR
158 RQPRSRQV	355 RVQAELDQV	275 KFLRHCESLR	450 GLINKDLTS
145 RRAAHSM	344 LLFTRYPDV	265 NRNFNSNILD	377 NL
141 WKVQ	327 IFGASQDTL	251 PNPVRTV	86 QIRLGSCPI
140 HWKVQ	319 NVPATITDI	243 VMPWLQYFPN	535 NLQAKETCQ
129 GRSMAFGHYS	316 DLENVPATI	209 CFGCRYSHDD	475 LSKMQLFLF
122 SFRVV	275 KFLRHCESL	205 MSAVCF	444 RFLDKDGLI
82 GDVF	272 ILDKFLRHC	203 NVMSAVCFG	334 TLSTALQWL

43 RRRQLRSAPP	268 FSNFILDKF	178 VALLVRGSAD	299 SAEKKAAGD
37 QRLLRQRRQ	203 NVMSAVCFG	155 FFTRQPRSQR	223 ELLSHNEEF
11 WPLNPLSIQQ	172 SEARELVAL	141 WKVQRRAAHS	188 GAFLDPRPL
518 VNVTLRESME	165 VLEGHVLSE	137 YSEHWKVQRR	179 ALLVRGSAD
504 NFSYGLTIKP	129 GRSMAFGHY	135 GHYSEHWKVQ	126 VSGGRSMAF
495 ANPNEPAKMN	69 AAHLSFARL	131 SMAFGHYSEH	77 LARRYGDVF
467 KRRCIGEELS	20 QTLLLRLS	127 SGGRSMAFGH	51 PPPGFAWPL
436 NPENFDPARF	524 ESMELLDSC	109 QQGSAFADRP	17 SIQQTTLLL
435 PNPNENFDPAR	509 LTIKPKSFK	107 LVQQGSAFAD	15 PLSIQQTTL
433 KWPNPENFDP	497 PNEPAKMNF	81 YGDVFQIRLG	364 VGRDRLPCM
429 HDPLKWPNP	461 MIFSVGKRR	72 LSFARLARRY	271 FILDKFLRH
424 QWSVNHDPLK	456 LTSRVMIFS	37 QRLLRQRRQ	190 FLDPPLTV
370 PCMGDQPNLP	409 VLGYHIPKD	35 VGQRLLRQRR	120 FASFRVVSG
348 RYPDVQTRVQ	397 VTIPHATTA	34 HVGQRLLRQRR	69 AAHLSFARL
307 DSHGGARLD	384 FLYEAMRFS	8 NDPWPLNPLS	515 SFKVNVTLR
290 RDMMDAFILS	364 VGRDRLPCM	5 LSPNDPWPLN	500 PAKMNFSYG
281 ESLRPGAAAPR	236 GAGSLVDVM	3 TSLSPNDPWPL	386 YEAMRFSSF
253 PVRTVFRFE	181 LVRGSADGA		344 LLFTRYPDV
251 PNPVRTVFR	126 VSGGRSMAF	HLA-B*1510 Nonamers	337 TALQWLLLL
227 HNEEFGRRTVG	125 VVSGGRSMA	Pos 1 2 3 4 5 6 7 8 9	282 SLRPGAAAPR
210 FGCRYSHDDP	112 SAFADRPAP	148 AHSMMRNFF	218 DPEFRELLS
209 CFGCRYSHDD	58 PLIGNAAAV	89 LGSCPIVVL	172 SEARELVAL
153 RNFFTRQPRS	28 SVLATVHVG	139 EHWKVQRR	76 RLARRYGDV
135 GHYSEHWKVQ	25 LLLSVLATV	438 ENFDPARFL	64 AAVGQAAHL
128 GGRSMAFGHY	24 LLLSVLAT	412 YHIPKDTVV	41 RQRRRQLRS
84 VFQIRLGSCP	532 AVQNLQAKE	361 DQVVGRDRL	448 KDGLINKDL
44 RRQLRSAPPG	492 DFRANPNEP	216 HDDPEFREL	336 STALQWLLL
42 QRRRQLRSAP	432 LKWPNPENF	32 TVHVGQRLL	331 SQDTLSTAL
36 GQRLLRQRR	421 FVNQWSVNH	514 KSFKVNVT	320 VPATITDIF
35 VGGQRLRQRR	419 VVFVNQWSV	308 SHGGGARLD	298 LSAEKKAAG
10 PWPLNPLSIQ	337 TALQWLLL	307 DSHGGARL	286 GAAPRDMMD
8 NDPWPLNPLS	324 ITDIFGASQ	215 SHDDPEFRE	276 FLRHCESLR
499 EPAKMNFSYG	233 RTVGAGSLV	188 GAFLDPRPL	269 SNFILDKFL
497 PNEPAKMNF	198 VVAVANVMS	172 SEARELVAL	253 PVRTVFRF
438 ENFDPARFLD	164 QVLEGHVL	81 YGDVFQIRL	250 FPNPVRTV
415 PKDTVVFVNQ	156 FTRQPRSQR	39 LLRQRRRQL	192 DPRPLTVVA
361 DQVVGRDRLP	89 LGSCPIVVL	521 TLRESMELL	140 HWKVQRRRAA
285 PGAAPRDMMD	76 RLARRYGDV	488 AHQCDFRAN	138 SEHWKVQRR
262 EQLNRNFSNF	64 AAVGQAAHL	474 ELSKMQFL	112 SAFADRPAP
167 EGHVLSEARE	19 QQTLLLLL	472 GEELSKMQL	106 ALVQQGSAF
260 EFEQLNRNFS	8 NDPWPLNPL	428 NHDPPLKWP	520 VTLRESMEL
52 PGPFAWPLIG	519 NVTLRESME	424 QWSVNHDPL	514 KSFKVNVT
301 EKKAAGDSHG	514 KSFKVNVT	402 ATTANTSVL	485 SILAHQCDF
HLA-A*0201 Octamers	483 FISILAHQC		472 GEELSKMQL
Pos 1 2 3 4 5 6 7 8	459 RVMIFSVGK	374 DQPNLPYVL	438 ENFDPARFL
531 SAVQNLQA	441 DPARFLDKD	327 IFGASQDTL	429 HDPLKWPNP
525 SSMELLDSC	437 PENFDPARF	278 RHCESLRPG	413 HIPKDTVVF
494 RANPNEPA	408 SVLGYHIPK	239 SLVDVMPWL	352 VQTRVQAE
	406 NTSQLGYHI	232 GRTVGAGSL	338 ALQWLLLL
	403 TTANTSVLG	226 SHNEEFGR	316 DLEENVPATI

488 AHQCDFRA	398 TIPHATTAN	173 EARELVALL	312 GARLDLENV
481 FLFISILA	390 RFSSFPVPT	169 HVLSEAREL	301 EKKAAGDSH
436 NPENFDPA	372 MGDQPNL PY	168 GHVLSEARE	264 LNRNFSNFI
398 TIPHATT A	370 PCMGDQPNL	158 RQPRS RQVL	263 QLN RNF SNF
395 VPVTIPHA	367 DRLPCM GDQ	103 IHQALVQQG	232 GRTVGAGSL
381 VLAFLYEA	362 QVVGRDRLP	22 TLLL LSVL	217 DDPEFRELL
376 PNLPYVLA	346 FTRYPDVQT	400 PHATTANTS	216 HDDPEFREL
351 DVQTRVQA	296 FILSAEKKA	370 PCMGDQPNL	169 HVLSEAREL
331 SQDTLSTA	250 FPNPVRTVF	337 TALQWLLL	115 ADRPAFASF
323 T1TDIFGA	229 EEFGRTVGA	334 LSTALQWL	89 LGSCPIVVL
315 LDLENVPA	213 RYSHDDPEF	309 HGGARLDL	74 FARLARRYG
306 GDSHGGGA	209 CFGCRYSHD	217 DDPEFRELL	46 QLRSAPP GP
298 LSAEKKA A	202 ANVMSAVCF	163 RQVLEGHVL	513 PKSFKVNV T
297 ILSAEKKA	182 VRGSADGAF	99 GERAIHQAL	452 INKDLTSRV
293 MDAFILSA	142 KVQRRAAHS	70 AHLSFARLA	443 ARFLDKDGL
288 APRDMMDA	107 LVQQGS AFA	69 AAHLSFARL	442 PARFLDKDG
281 ESLRPGAA	93 PIVVNLGER	51 PPGPFAWPL	424 QWSVNHDPL
280 CESLRPGA	54 PFAWPLIGN	33 VHVGQRLLR	361 DQVVGRDRL
230 EFGRTVGA	18 IQQTLLL	31 ATVHVGQRL	327 IFGASQDTL
200 AVANVMSA	16 LSIQQTLL	18 IQQTLLL	309 HGGARLDL
195 PLTVVAVA	12 PLNPLSIQ Q	15 PLSIQQTLL	265 NRNF SNFIL
193 PRPLTVVA	515 SFKVNVTLR	528 LLD SAVQNL	262 EQLN RNF SN
182 VRGSADGA	495 ANPNEPAKM	520 VTLRESMEL	229 EEFGRTVGA
179 ALLVRGSA	472 GEELSKMQL	479 QLFLFISIL	163 RQVLEGHVL
172 SEARELVA	464 SVGKRR CIG	467 KRRCIGEEL	81 YGDVFQIRL
167 EGHVLSEA	450 GLINKDLTS	443 ARFLDKDGL	32 TVHVGQRLL
141 WKVQRRAA	443 ARFLDKDGL	413 HIPKDTVVF	18 IQQTLLL
140 HWKVQRRA	431 PLKWPNPEN	352 VQTRVQAE L	501 AKMNFSYGL
126 VSGGRSMA	426 SVNHDP LKW	336 STALQWLL	498 NEPAKMNF S
114 FADRP AFA	418 TVVFVNQWS	331 SQDTLSTAL	464 SVGKRR CIG
112 SAFADRP A	396 PVTIPHATT	260 EFEQLN RNF	446 LDKDGLINK
108 VQQGS AFA	378 LPYVLAFLY	256 TVFREFEQL	412 YHIPKDTVV
106 ALVQQGSA	353 QTRVQAELD	250 FPNPVRTVF	402 ATTANTS VL
99 GERAIHQ A	331 SQDTLSTAL	183 RGSADG AFL	374 DQPNLPYVL
95 VVLNGERA	320 VPATITDIF	135 GHYSEHWKV	370 PCMGDQPNL
71 HLSFARLA	294 DAFILSAEK	64 AAVGQA AHL	351 DVQTRVQAE
68 QAAHLSFA	291 DMMDAFILS	17 SIQQTLLL	335 LSTALQWLL
63 AAVGQAA	282 SLRPGAA PR	16 LSIQQTLL	307 DSHGGARL
62 NAAAVGQA	269 SNFILDKFL	8 NDPWPLNPL	300 AEKKAAGDS
58 PLIGNAAA	255 RTVFR EFEQ	5 LSPNDPWPL	290 RDMMDAFIL
57 WPLIGNAA	249 YFPNPVRTV	501 AKMNFSYGL	280 CESLRPGAA
56 AWPLIGNA	241 VDVM PWLQY	497 PNEPAKMNF	275 KFLRH CESL
49 SAPP GPFA	240 LVDVM PWLQ	462 IFSVGKRR C	274 DKFLRH CES
43 RRRQLRSA	206 SAVCFG CRY	453 NKDLTSRV M	273 LDKFLRH CE
24 LLLL SVLA	190 FLDPRPLTV	448 KDGLINKDL	256 TVFREFEQL
	158 RQPRS RQVL	432 LKWPNPENF	251 PNPVRTVFR
HLA-A*0202 Nonamers			
Pos 1 2 3 4 5 6 7 8 9	96 VLNGERA IH	377 NLPYVLAFL	220 EFRELLSHN
535 NLQAKETCQ	95 VVLNGERA I	376 PNLPYVLA F	183 RGSADG AFL
529 LDSAVQNLQ	94 IVVLNGERA	335 LSTALQWLL	158 RQPRS RQVL
498 NEPAKMNF S	84 VFQIRLGSC	290 RDMMDAFIL	149 HSMMRN FFT
492 DFRANPNEP	66 VGQAAHLS F	275 KFLRH CESL	147 AAHSMMRNF
485 SILAHQCDF	65 AVGQAAHLS	269 SNFILDKFL	97 LNGERA IHQ
440 FDPARFLDK	59 LIGNAAAVG	265 NRNF SNFIL	31 ATVHVGQRL
402 ATTANTS VL	46 QLRSAPP GP	236 GAGSLVDVM	19 QQTTLLL
399 IPHATTANT	29 VLATVHVGQ	19 QQTTLLL	16 LSIQQTLL
385 LYEA MRFSS	4 SLSPNDPWP	437 PENFDPARF	8 NDPWPLNPL
	2 GTSLSPNPD	288 APRDMMDAF	5 LSPNDPWPL
	518 VNVTLRESM	285 PGAAPRDMM	527 ELLD SAVQN

380 YVLAFLYEA	504 NFSYGLTIK	284 RPGAAPRDM	519 NVTLRESME
355 RVQAELDQV	486 ILAHQCDFR	253 PVRTVFREF	499 EPAKMNF SY
335 LSTALQWLL	445 FLDKDGLIN	213 RYSHDDPEF	496 NPNEPAKMN
327 IFGASQDTL	368 RLPCM GDQP	197 TVVAVANVM	481 FLFISILAH
319 NVPATITDI	363 VVGRDRLPC	147 AAHSMMRN F	466 GKRR CIGEE
310 GGGARLDLE	352 VQTRVQAE L	124 RVVSGGRSM	440 FDPARFLDK
302 KKAAGDSHG	314 RLDLENVPA	112 SAFADRP AF	409 VLGYHIPKD
301 EKKAAGDSH	309 HGGGARLDL	47 LRSAPP GP F	384 FLYEAMRFS
297 ILSAEKKAA	295 AFILSAEK K	508 GLTIKP KSF	359 ELDQVVGRD
292 MMDAFILSA	285 PGAAPRDM M	473 EELSKMQLF	346 FTRYPDVQT
285 PGAAPRDM M	267 NFSNFI LDK	386 YEAMRFSS F	314 RLDLENVPA
284 RPGAAPRDM	259 REFEQLN RN	383 AFLYEAMRF	310 GGGARLDLE
234 TVGAGSLVD	234 TVGAGSLVD	381 VLAFLYEAM	297 ILSAEKKAA
204 VMSAVCFGC	207 AVCFG CRY S	364 VGRDRLPCM	260 EFEQLNRNF
199 VAVANVMSA	195 PLTVVAVAN	248 QYFPNPV RT	257 VFREFEQLN
197 TVVAVANV M	192 DPRPLTVVA	242 DVMPWLQYF	255 RTVFREFEQ
186 ADGAFLDPR	188 GAFLDPRPL	223 ELLSHNEEF	195 PLTVVAVAN
183 RGSADGAFL	187 DGAFLDPRP	202 ANVMSAVCF	176 ELVALLVRG
176 ELVALLVRG	179 ALLVRGSAD	126 VSGGRSMAF	170 VLSEARELV
171 LSEARELVA	170 VLSEARELV	115 ADRPAFASF	141 WKVQRRAAH
145 RRRAAHSMR	154 NFFTRQPRS	106 ALVQQGS AF	122 SFRVVSGGR
144 QRRAAHSM M	148 AHSMMRN FF	77 LARRYGDVF	84 VFQIRLGSC
130 RSMAFGHYS	144 QRRAAHSM M	518 VNVTLRESM	44 RRQLRSAPP
118 PAFASFRVV	132 MAFGHYSEH	495 ANPNEPAK M	37 QRLLRQRR
116 DRPAFASFR	99 GERAIHQAL	470 CIGEELSKM	34 HVGQRLLRQ
112 SAFADRP AF	86 QIRLGSCPI	455 DLTSRVMIF	24 LLLL SVLAT
110 QGSFADRP	81 YGDVFQIRL	320 VPATITDIF	490 QCDFRANPN
103 IHQALVQ QG	77 LARRYGDVF	263 QLN RNF SNF	476 SKMQLFLFI
99 GERAIHQAL	51 PPGPFAWPL	182 VRGSADGAF	457 TSRVMIFS V
75 ARLARRYGD	47 LRSAPP GP F	485 SILAHQCD F	395 VPVTIPHAT
72 LSFARLARR	38 RLLRQRRR Q	475 LSKMQLFLF	391 FSSFVPVTI
67 QAAHLSFA	23 LLLL SVLA	414 IPKDTVV FV	381 VLAFLYEAM
66 VGQAAHLSF	9 DPWPLNPLS	349 YPDVQTRVQ	376 PNLPYVLAF
62 NAAAVGQAA	535 NLQAKETCQ	338 ALQWLLL LF	375 QPNLPYVLA
61 GNAAAVGQA	530 DSAVQNLQA	268 FSNFILDKF	362 QVGRDRLP
60 IGNAAAVGQ	501 AKMNFSYGL	249 YFPNPV RTV	211 GCRYSHDDP
53 GPFAWPLIG	467 KRR CIGEE I	192 DPRPLTVVA	209 CFGCRYSHD
47 LRSAPP GP F	453 NKDLTSRVM	144 QRRAAHSM M	182 VRGSADGAF
28 SVLATVHVG	439 NFDPARFLD	143 VQRRRAAHSM	171 LSEARELVA
	389 MRFSSFV PV	119 AFASFRVVS	165 VLEGHVLSE
HLA-A*0202 Decamers	335 LSTALQWLL	90 GSCPIVV LN	157 TRQPRS RQV
Pos 1234567890	297 ILSAEKKAA	66 VGQAAHLSF	154 NFFTRQPRS
	276 FLRH CESLR	511 IKPKSFKVN	142 KVQRRAAH S
63 AAAVGQAAHL	274 DKFLRH CES	494 RANPNEPAK	113 AFADRP AFA
303 KAAGDSHGGG	265 NRRNFSN FIL	452 INKDLTSRV	95 VVLNGERA I
286 GAAPRDMMDA	257 VFREFEQLN	391 FSSFVPVTI	78 ARRYGDVFQ
146 RAAHSMMRN F	235 VGAGSLV DV	390 RFSSFVPVT	75 ARLARRYGD
68 QAAHLSFARL	232 GRTVGAGSL	373 GDQPNLPYV	72 LSFARLARR
62 NAAAVGQAAH	183 RGSADGAFL	359 ELDQVVGRD	71 HLSFARLAR
200 AVANVMSAVC	180 LLVRGSADG	357 QAEILDQVVG	57 WPLIGNAAA
119 AFASFRVVSG	143 VQRRAAHSM	347 TRYPDVQTR	40 LRQR RRQLR
113 AFADRP AFA S	119 AFASFRVVS	315 LDLENVPAT	36 GQRLLRQRR
530 DSAVQNLQAK	113 AFADRP AFA	297 ILSAEKKAA	29 VLATVHVGQ
499 EPAKMNF SYG	88 RLGSCPIVV	272 ILDKFLRHC	23 LLLL SVLA
493 FRANPNEPAK	71 HLSFARLAR	228 NEEFGRTVG	6 SPNDPWPLN

486 ILAHQCDFRA	26 LLSVLATVH	227 HNEEFGRTV	4 SLSPNDPWP
441 DPARFLDKDG	5 LSPNDPWPL	176 ELVALLVRG	531 SAVQNLQAK
403 TTANTSVLGY	460 VMIFSVGKR	157 TRQPRSRQV	492 DFRANPNEP
400 PHATTANTSV	448 KDGLINKDL	156 FTRQPRSRQ	486 ILAHQCDFR
386 YEAMRFSSFV	444 RFLDKDGLI	140 HWKVQRRAA	454 KDLTSRVMI
381 VLAFLYEAMR	424 QWSVNHDPL	137 YSEHWKVQR	445 FLDKDGLIN
356 VQAELDQVVG	420 VFVNQWSVN	94 IVVLNGERA	436 NPENFDPAR
336 STALQWLLLL	393 SFVPVTIPH	73 SFARLARRY	434 WPNPENFDP
328 FGASQDTLST	358 AELDQVVGR	49 SAPPGPFAW	406 NTSVLGYHI
320 VPATITDIFG	343 LLLFTRYPD	48 RSAPPGPFA	399 IPHATTANT
311 GGARLDENV	342 LLLLFRYP	38 RLLRQRRQQ	383 AFLYEAMRF
304 AAGDSHGGGA	318 ENVPATITD	4 SLSPNDPWP	378 LPYVLAFLY
302 KKAAGDSHGG	315 LDLENVPAT	527 ELDSAQVN	366 RDRLPCMGD
298 LSAEKKAAGD	301 EKKAAGDSH	517 KVNVTLRES	353 QTRVQAELD
293 MDAFILSAEK	290 RDMMDAFIL	513 PKSFKVNV	349 YPDVQTRVQ
287 AAPRDMMDA	284 RPGAAPRDM	471 IGEELSKMQ	342 LLLLFRYP
285 PGAAAPRDMMD	281 ESLRPGAAP	463 FSVGKRRCI	341 WLLLFRTRY
235 VGAGSLVDVM	270 NFILDKFLR	411 GYHIPKDTV	319 NVPATITDI
205 MSAVCFGCRY	246 WLQYFPNPV	403 TTANTSVLG	272 ILDKFLRHC
198 VVAVANVMSA	224 LLSHNEEFG	384 FLYEAMRFS	268 FSNFILDKF
187 DGAFLDPRPL	189 AFLDPRPLT	358 AELDQVVGR	252 NPVRTVFR
184 GSADGAFLDP	167 EGHVLSEAR	356 VQAELDQVV	246 WLQYFPNPV
177 LVALLVRGSA	163 RQVLEGHVL	350 PDVQTRVQA	244 MPWLQYFPN
172 SEARELVAL	155 FFTRQPRSR	318 ENVPATITD	231 FGRTVGAGS
147 AAHSMMRNFF	146 RAAHSMMRN	306 GDSHGGAR	213 RYSHDDPEF
145 RRAAHSMMRN	139 EHWKVQRRA	298 LSAEKKAAG	202 ANVMSAVCF
131 SMAFGHYSEH	121 ASFRVVSGG	286 GAAPRDMMD	194 RPLTVVAVA
117 RPAFASFRVV	116 DRPAFASFR	283 LRPGAAPRD	156 FTRQPRSRQ
111 GSAFADRPAF	100 ERAIHQALV	247 LQYFPNPV	143 VQRRAAHSM
104 HQALVQQGSA	72 LSFARLARR	235 VGAGSLVDV	128 GGRSMAFGH
100 ERAIHQALVQ	55 FAWPLIGNA	234 TVGAGSLVD	96 VLNGERAIH
76 RLARRYGDVF	50 APPGPFAWP	229 EEFGRTVGA	93 PIVVLNGER
73 SFARLARRYG	13 LNPLSIQQT	198 VVAVANVMS	92 CPIVVLNGE
69 AAHLSFARLA	531 SAVQNLQAK	195 PLTVVAVAN	79 RRYGDVFQI
67 GQAAHLSFAR	511 IKPKSFKVN	193 PRPLTVVAV	66 VGQAAHLSF
64 AAVGQAAHLS	462 IFSVGKRR	190 FLDPRPLTV	58 PLIGNAAAV
61 GNAAAVGQAA	446 LDKDGLINK	189 AFLDPRPLT	53 GPFAWPLIG
54 PFAWPLIGNA	435 PNPNFDPA	187 DGAFLDPRP	49 SAPPGPFAW
48 RSAPPGPFAW	430 DPLKWPNP	184 GSADGAFLD	43 RRRQLRSAP
29 VLATVHVGQR	414 IPKDTVVVF	177 LVALLVRGS	26 LLSVLATVH
531 SAVQNLQAKE	387 EAMRFSSFV	164 QVLEGHVL	10 PWPLNPLSI
500 PAKMNFSYGL	373 GDQPNLPYV	146 RAAHSMMRN	9 DPWPLNPLS
494 RANPNEPAKM	347 TRYDPVQTR	136 HYSEHWKVQ	503 MNFSYGLTI
487 LAHQCDFRAN	293 MDAFILSAE	125 VVSGGRSMA	497 PNEPAKMNF
442 PARFLDKDGL	278 RHCESLRPG	120 FASFRVVSG	478 MQLFLFISI
404 TANTSVLGYH	266 RNFSNFI	118 PAFASFRVV	470 CIGEELSKM
401 HATTANTSV	262 EQLNRFNSN	111 GSAFADRPA	441 DPARFLDKD
387 EAMRFSSFVP	245 PWLQYFPNP	95 VVLNGERAI	437 PENFDPARF
382 LAFLYEAMRF	226 SHNEEFGR	87 IRLGSCPIV	432 LKWPNPENF
357 QAEILDQVVGR	219 PEFRELLSH	82 GDVFQIRLG	430 DPLKWPNP
337 TALQWLLLL	193 PRPLTVVAV	63 AAAVGQAAH	401 HATTANTS
329 GASQDTLSTA	185 SADGAFLDP	60 IGNAAAVGQ	388 AMRFSSFVP
321 PATITDIFG	138 SEHWKVQRR	37 QRLLRQRR	387 EAMRFSSFV
312 GARLDENV	133 AFGHYSEHW	36 GQRLLRQRR	369 LPCMGDQPN
299 SAEKKAAGDS	122 SFRVVSGGR	26 LLSVLATVH	368 RLPCMGDQP
294 DAFILSAEKK	118 PAFASFRVV	534 QNLQAKETC	357 QAEILDQVVG

236 GAGSLVDVMP	103 IHQALVQQG	531 SAVQNLQAK	343 LLLFTRYPD
206 SAVCFGCRYS	92 CPIVVLNGE	515 SFKVNVTLR	296 FILSAEKKA
201 VANVMSAVCF	90 GSCPIVVLN	512 KPKSFKVNV	289 PRDMMDAFI
199 VAVANVMSAV	79 RRYGDVFQI	510 TIKPKSFKV	284 RPGAAPRDM
188 GAFLDPRPLT	500 PAKMNF SYG	509 LTIKPKSFK	242 DVMPWLQYF
185 SADGAFLDPR	498 NEPAKMNFS	507 YGLTIKPKS	236 GAGSLVDVM
178 VALLVRGSA	480 LFLFISILA	499 EPAKMNF SY	224 LLSHNEEFG
173 EARELVALLV	478 MQLFLFISI	492 DFRANPNEP	206 SAVCFGCRY
132 MAFGHYSEHW	476 SKMQLFLFI	487 LAHQCDFRA	201 VANVMSAVC
120 FASFRVVS	449 DGLINKDLT	486 ILAHQCDFR	199 VAVANVMSA
118 PAFASFRVVS	422 VNQWSVNHD	466 GKRRRCIGEE	185 SADGAFLDP
114 FADRPAPAFAS	416 KDTVVVFVNQ	457 TSRVMIFSV	181 LVRGSA
112 SAFADRPAPAF	392 SSFVPTV	454 KDLTSRVM	180 LLVVRGSA
105 QALVQQGSAF	345 LFTRYPDVQ	439 NFDPARFLD	178 VALLVRGSA
101 RAIHQALVQQ	330 ASQDTLSTA	436 NPENFDPAR	161 RSROVLEGH
77 LARRYGDVFQ	298 LSAEKKAAG	431 PLKWPNPEN	151 MMRNFFTRQ
74 FARLARRYGD	292 MMDAFILSA	421 FVNQWSVNHD	148 AHSMMRNFF
55 FAWPLIGNAA	287 AAPRDMMDA	416 KDTVVVFVNQ	144 QRRAAHSM
49 SAPPGPFAWP	248 QYFPNPV	415 PKDTVVVFVN	117 RPAFASFRV
30 LATVHVGQRL	218 DPEFRELLS	397 VTIPHATTA	114 FADRPAPAFAS
532 AVQNLQAKET	199 VAVANVMSA	394 FVPTV	88 RLGSPIVV
501 AKMNF SYGLT	166 LEGHVLSEA	392 SSFVPTV	63 AAAVGQAAH
495 ANPNEPAKMN	161 RSRQVLEGH	375 QPNLPYVLA	55 FAWPLIGNA
488 AHQCDFRANP	160 PRSRQVLEG	367 DRLPCMGDQ	52 PGPFAWPLI
443 ARFLDKDGLI	127 SGGRSMAFG	362 QVVGRDRLP	50 APPGPFAWP
405 ANTSVLGYHI	120 FASFRVVS	360 LDQVVGRDR	47 LRSAPPGP
402 ATTANTSVLG	109 QQGSAFADR	348 RYPDVQTRV	42 QRRRQLRSA
388 AMRFSSFV	91 SCPIVVLNG	346 FTRYPDVQT	38 RLLRQRRRQ
383 AFLYEAMRFS	80 RYGDVFQIR	345 LFTRYPDVQ	30 LATVHVGQR
358 AELDQVVG	67 GQAHL	329 GASQDTLST	25 LLLSVLATV
338 ALQWLLLFT	61 GNAAVGQA	323 TITDIFGAS	14 NPLSIQQTT
330 ASQDTLSTA	42 QRRRQLRSA	316 DLENVPATI	12 PLNPLSIQQ
322 ATITDIFGAS	35 VGQRLLRQR	313 ARLDLENVP	11 WPLNPLSIQ
313 ARLDLENVP	513 PKSFKVNT	311 GGARLDLEN	506 SYGLTIKPK
305 AGDSHGGGAR	502 KMNFSYGLT	282 SLRPGAAPR	494 RANPNEPAK
300 AEKKAAGDSH	488 AHQCDFRAN	281 ESLRPGAAP	483 FISILAHQC
295 AFILSAEKKA	469 RCIGEELSK	280 CESLRPGAA	461 MIFSVGKRR
288 APRDMMDAFI	466 GKRRRCIGEE	279 HCESLRPGA	404 TANTSVLGY
237 AGSLVDVMPW	458 SRVMIFSV	271 FILDKFLRH	398 TIPHATTAN
207 AVCFGCRYS	457 TSRVMIFSV	259 REFEQLNRR	382 LAFLYEAMR
202 ANVMSAVCFG	452 INKDLTSRV	252 NPVRTV	329 GASQDTLST
189 AFLDPRPLTV	440 FDPARFLDK	251 PNPVRTV	323 TITDIFGAS
186 ADGAFLDPRP	427 VNHDPLKWP	238 GSLVDVMPW	294 DAFILSAEK
179 ALLVRGSA	415 PKDTVVVFVN	237 AGSLVDVMP	132 MAFGHYSEH
174 ARELVALLVR	412 YHIPKDTVV	230 EFGRTV	105 QALVQQGSA
148 AHSMMRNFF	405 ANTSVLGYH	214 YSHDDPEFR	102 AIHQALVQQ
133 AFGHYSEHWK	375 QPNLPYVLA	207 AVCFGCRYS	68 QAAHLSFAR
121 ASFRVVS	356 VQAELDQVV	201 VANVMSAVC	62 AAAVGQAA
115 ADRPAFASFR	340 QWLLLFT	200 AVANVMSAV	533 VQNLQAKET
106 ALVQQGSAFA	339 LQWLLLFT	194 RPLTVVAVA	525 SMELLD
102 AIHQALVQQG	312 GARLDENV	191 LDPRPLTVV	524 ESMELLD
78 ARRYGDVFQI	286 GAAPRDMMD	175 RELVALLVR	487 LAHQCD
75 ARLARRYGD	283 LRPGAAPRD	171 LSEARELVA	471 IGEELSKM
70 AHLSFARLAR	252 NPVRTV	170 VLSEAREL	451 LINKDLTSR
65 AVGQAAHLSF	244 MPWLQYFPN	167 EGHVLSEAR	392 SSFVPTV
56 AWPLIGNAAA	238 GSLVDVMPW	165 VLEGHVLSE	326 DIFGASQDT
50 APPGPFAWPL	208 VCFGCRYS	160 PRSRQVLEG	321 PATITDIFG
31 ATVHVGQRL	205 MSAVCFGCR	155 FFTRQPRSR	315 LDLENVPAT

	194 RPLTVVAVA	154 NFFTRQPRS	304 AAGDSHGGG
HLA-A*0203 Nonamers			
Pos 1 2 3 4 5 6 7 8 9			
62 NAAAVGQAA	191 LDPRPLTVV	141 WKVQRRAAH	303 KAAGDSHGG
113 AFADRPAFA	151 MMRNFFTRQ	138 SEHWKVQRR	287 APPRDMMDA
530 DSAVQNLQA	98 NGERAIHQA	123 FRVVSGGRS	230 EFGRTVGAG
493 FRANPNEPA	82 GDVFQIRLG	117 RPAFASFRV	226 SHNEEFGRT
287 AAPRDMMDA	30 LATVHVGQR	113 AFADRPAFA	198 VVAVANVMS
111 GSAFADRPA	11 WPLNPLSIQ	110 QGSAFADRP	193 PRPLTVVAV
67 GQAAHLSFA	523 RESMELLDS	102 AIHQALVQQ	167 EGHVLSEAR
61 GNAAAVGQA	512 KPKSFKVNV	88 RLGSCPIVV	146 RAAHSMMRN
48 RSAPPGPFA	506 SYGLTIKPK	78 ARRYGDVFQ	136 HYSEHWKVQ
487 LAHQCDFRA	505 FSYGLTIKP	74 FARLARRYG	118 PAFASFRVV
199 VAVANVMSA	494 RANPNEPAK	71 HLSFARLAR	101 RAIHQALVQ
178 VALLVRGSA	491 CDFRANPNE	61 GNAAAVGQA	59 LIGNAAAVG
105 QALVQQGSA	477 KMQLFLFIS	58 PLIGNAAAV	394 FVPVTIPHA
55 FAWPLIGNA	471 IGEELSKMQ	55 FAWPLIGNA	356 VQAELDQVV
330 ASQDTLSTA	429 HDPLKWPNP	43 RRRQLRSAP	281 ESLRPGAAP
322 ATIDIFGA	428 NHDPLKWPN	34 HVGQRLLRQ	238 GSLVDVMPW
305 AGDSHGGGA	407 TSVLGYHIP	29 VLATVHVGQ	227 HNEEFGRTV
70 AHLSFARLA	382 LAFLYEAMR	28 SVLATVHVG	164 QVLEGHVL
56 AWPLIGNAA	379 PYVLAFLYE	9 DPWPLNPLS	162 SRQVLEGHV
524 ESMELLDSA	325 TDIFGASQD	7 PNDPWPLNP	91 SCPIVVLNG
480 LFLFISILA	310 GGGARLDLE	6 SPNDPWPLN	90 GSCPIVVLN
435 PNPNENFDPA	303 KAAGDSHGG	2 GTSLSPNDP	28 SVLATVHVG
397 VTIPHATTA	299 SAEKKAAGD	530 DSAVQNLQA	530 DSAVQNLQA
394 FVPVTIPHA	279 HCESLRPGA	526 MELLDLSAVQ	517 KVNVTLRES
380 YVLAFLYE	186 ADGAFLDPR	525 SMELLDLSAV	511 IKPKSFKVN
375 QPNLPYVLA	175 RELVALLVR	524 ESMELLDSA	493 FRANPNEPA
350 PDVQTRVQA	150 SMMRNFFTR	516 FKVNVTLRE	484 ISILAHQCD
314 RLDLENVPA	108 VQQGSAFAD	504 NFSYGLTIK	462 IFSGVKRRC
297 ILSAEKKAA	87 IRLGSCPIV	496 NPNEPAKMN	460 VMIFSVGKR
296 FILSAEKKA	85 FQIRLGSCP	493 FRANPNEPA	458 SRVMIFSVG
292 MMDAFILSA	49 SAPPGPFAW	489 HQCDFRANP	435 PNPNENFDPA
280 CESLRPGAA	48 RSAPPGPFA	484 ISILAHQCD	427 VNHDPLKWP
279 HCESLRPGA	43 RRRQLRSAP	481 FLFISILAH	426 SVNHDPLKW
229 EEFGRTVGA	7 PNDPWPLNP	464 SVGKRRCIG	422 VNQWSVNH
194 RPLTVVAVA	1 MGTSLSPND	461 MIFSVGKRR	421 FVNQWSVNH
192 DPRPLTVVA	525 SMELLDLSAV	459 RVMIFSVGK	419 VVFVNQWSV
181 LVRGSADGA	503 MNFSYGLTI	458 SRVMIFSVG	417 DTVVVFVNQW
171 LSEARELVA	496 NPNEPAKMN	456 LTSRVMIFS	416 KDTVVVFVNQ
166 LEGHVLSEA	489 HQCDFRANP	450 GLINKDLTS	408 SVLGYHIPK
140 HWKVQRRAA	484 ISILAHQCD	449 DGLINKDLT	393 SFVPVTIPH
139 EHWKVQRRA	463 FSVGKRRCI	447 DKDGLINKD	358 AELDQVVGR
125 VVSGGRSMA	454 KDLTSRVM	446 LDKDGLINK	318 ENVPATITD
107 LVQQGSAFA	365 GRDRLPCM	435 PNPNENFDPA	311 GGARLDLEN
98 NGERAIHQA	350 PDVQTRVQA	434 WPNPNENFDP	308 SHGGGARLD
94 IVVLNGERA	348 RYPDQVTRV	430 DPLKWPNP	306 GDSHGGGAR
57 WPLIGNAAA	328 FGASQDTLS	427 VNHDPLKWP	278 RHCESLRPG
42 QRRQLRSA	311 GGARLDLEN	420 VFVNQWSV	261 FEQLNRNFS
23 LLLLLSVLA	305 AGDSHGGGA	419 VVFVNQWSV	259 REFEQLNRN
63 AAAVGQAAH	304 AAGDSHGGG	417 DTVVFVNQW	254 VRTVFREFE
303 KAAGDSHGG	302 KKAAGDSHG	409 VLGYHIPKD	237 AGSLVDVMP
286 GAAPRDMMD	215 SHDDPEFRE	407 TSVLGYHIP	235 VGAGSLVVD
146 RAAHSMMRN	168 GHVLSEARE	406 NTSVLGYHI	222 RELLSHNEE
68 QAAHLSFAR	157 TROPRSRQV	404 TANTSVLGY	221 FRELLSHNE
200 AVANVMSAV	153 RNFFTRQPR	399IPHATTANT	215 SHDDPEFRE
	145 RRAAHSMR	398 TIPHATTAN	196 LTVVAVANV
	141 WKVQRRAAH	396 PVTIPHATT	177 LVALLVRGS
	140 HWKVQRRAAH	395 VPVTIPHAT	168 GHVLSEARE

119 AFASFRVVS	104 HQALVQQGS	393 SFVPVTIPH	160 PRSRQVLEG
499 EPAKMNF SY	101 RAIHQALVQ	389 MRFSSFVPV	150 SMMRNFFTR
486 ILAHQCDFR	97 LNGERAIHQ	388 AMRFSSFVP	139 EHWKVQRRA
441 DPARFLDKD	68 QAAHLSFAR	385 LYEA MRFSS	134 FGHYSEHWK
403 TTANTSVLG	63 AAAVGQAAH	380 YVLAFLYE A	131 SMAFGHYSE
400 PHATTANTS	62 AAAVGQAA	372 MG DQPNLPY	127 SGGRSMAFG
386 YEAMRFSSF	36 GQRLLRQRR	371 CMGDQPNLP	123 FRVVSGGRS
381 VLAFLYEAM	33 VHVGQRLLR	365 GRDRLPCM G	108 VQQGSAFAD
356 VQAELDQVV	533 VQNLQAKET	354 TRVQAELDQ	104 HQALVQQGS
336 STALQWLLL	507 YGLTIKP KS	351 DVQTRVQAE	103 IHQALVQQG
328 FGASQDTLS	487 LAHQCDFRA	342 LLLLFTTRY	100 ERAIHQALV
320 VPATITDIF	465 VGKRR CIGE	341 WLLLFTTRY	94 IVVLNGERA
311 GGARLDLEN	436 NPENFDPAR	330 ASQDTLSTA	82 GDVFQIRLG
304 AAGDSHGGG	434 WPNPENFDP	325 TDIFGASQD	73 SFARLARRY
302 KKAAGDSHG	399 IPHATTANT	324 ITDIFGASQ	61 GNAAAVGQA
298 LSAEKKAAG	371 CMGDQPNLP	317 LENVPATIT	60 IGNAAAVGQ
293 MDAFILSAE	366 RDRLPCM GD	314 RLDLENVPA	56 AWPLIGNAA
285 PGAAPRDMM	349 YPDVQTRVQ	303 KAAGDSHGG	27 LSVLATVHV
235 VGAGSLVDV	332 QDTLSTALQ	302 KKAAGDSHG	13 LNPLSIQQT
205 MSAVCFGCR	329 GASQDTLST	299 SAEKKAAGD	2 GTSLSPNDP
198 VVAVANVMS	313 ARLDLENVP	293 MDAFILSAE	526 MELLD SAVQ
187 DGAFLDPRP	308 SHGGGARLD	277 LRHCESLRP	518 VNVTLRESM
184 GSADGAFLD	300 AEKKAAGDS	267 NFSNFILDK	516 FKVNVTLRE
177 LVALLVRGS	289 PRDMMMDAFI	261 FEQLNRNFS	505 FSYGLTIKP
172 SEARELVAL	273 LDKFLRHCE	254 VRTVFR EFE	504 FSYGLTIK
147 AAHSMMRNF	251 PNPVRTVFR	245 PWLQYFPNP	491 CDFRANPNE
145 RRAAHSMMR	243 VMPWLQYFP	240 LVDVMPWLQ	489 HQCDFRANP
131 SMAFGHYSE	237 AGSLVDVMP	224 LLSHNEEFG	488 AHQCDFRAN
117 RPAFASFRV	231 FGRTVAGAGS	220 EFR ELLSHN	477 KMQLFLFIS
104 HQALVQQGS	227 HNEEFGRTV	208 VCFG CRYSH	459 RVMIFS VVGK
100 ERAIHQALV	222 RE LL SHNEE	206 SAVCFG CRY	453 NKDLTSRVM
76 RLARRYGDV	221 FRELLSHNE	205 MSAVCFGCR	447 DKDGLINKD
73 SFARLARRY	184 GSADGAFLD	199 VAVANVMSA	423 NQWSVNHD P
69 AAHLSFARL	162 SRQVLEGHV	196 LTVVAVANV	420 VFVNQWSVN
64 AAVGQAAHL	159 QPRSRQVLE	179 ALLVRGSAD	418 TVVFVNQWS
54 PFAWPLIGN	137 YSEHWKVQR	159 QPRSRQVLE	415 PKDTVVFVN
29 VLATVHVGQ	136 HYSEHWKVQ	152 MRNFFTRQP	411 GYHIPKDTV
531 SAVQNLQAK	135 GHYSEHWKV	151 MMRNFFTRQ	410 LGYHIPKDT
500 PAKMNF SYG	131 SMAFGHYSE	150 SMMRNFFTR	407 TSVLGYHIP
494 RANPNEPAK	128 GGRSMAFGH	132 MAFGHYSEH	403 TTANTSVLG
442 PARFLDKDG	123 FRVVSGGRS	131 SMAFGHYSE	397 VTIPHATTA
404 TANTSVLGY	117 RPAFASFRV	129 GRSMAFGHY	390 RFSSFVPVT
401 HATTANTS V	114 FADRPAPAS	114 FADRPAPAS	389 MRFSSFVPV
387 EAMRFSSFV	105 QALVQQGSA	108 VQQGSAFAD	380 YVLAFLYE A
382 LAFLYEAMR	60 IGNAAAVGQ	107 LVQQGSAFA	379 PYVLAFLYE
357 QAELDQVVG	57 WPLIGNAAA	101 RAIHQALVQ	373 GDQPNLPYV
337 TALQWLLL	56 AWPLIGNAA	100 ERAIHQALV	372 MG DQPNLPY
329 GASQDTLST	53 GPF AWP LIG	98 NGERAIHQ A	365 GRDRLPCM G
321 PATITDIFG	52 PGPF AWP L	96 VLNGERAIH	363 VVGRDRLPC
312 GARLDLENV	45 RQLRSAPP G	93 PIVVLNGER	360 LDQVVGRDR
299 SAEKKAAGD	27 LSVLATVHV	83 DVFQIRLGS	350 PDVQTRVQA
294 DAFILSAEK	14 NPLSIQQT	79 RRYGDVFQI	347 TRYPDVQTR
236 GAGSLVDVM	10 PWPLNPLSI	72 LSFARLARR	340 QWLLLLFT
206 SAVCFG CRY	6 SPNDPWPLN	68 QAAHLSFAR	339 LQWLLLLFT
201 VANVMSAVC	534 QNLQAKETC	67 GQAAHLSFA	332 QDTLSTALQ
188 GAFLDPRPL	526 MELLD SAVQ	62 NAAAVGQAA	328 FGASQDTLS
185 SADGAFLDP	522 LRESMELLD	59 LIGNAAAVG	324 ITDIFGASQ
173 EARELVALL	516 FKVNVTLRE	57 WPLIGNAAA	322 ATITDIFGA
132 MAFGHYSEH	493 FRANPNEPA	54 PFAWPLIGN	317 LENVPATIT

120 FASFRVVSG	490 QCDFRANPN	53 GPF AWP LIG	295 AFILSAEKK			
118 PAFASFRVV	442 PARFLDKDG	50 APPGPFAWP	293 MDAFILSAE			
114 FADRPAFAS	433 KWPNPENFD	46 QLRSAPPGP	292 MMDFILSA			
112 SAFADRPAF	425 WSVNHDPLK	42 QRRRQLRSA	279 HCESLRPGA			
101 RAIHQALVQ	423 NQWSVNHDHP	41 RQRRRQLRS	270 NFILDKFLR			
77 LARRYGDVF	401 HATTANTS	35 VGQRLLRQR	267 NFSNFILDK			
74 FARLARRYG	400 PHATTANTS	30 LATVHVGQR	258 FREFEQLNR			
49 SAPPGPFAW	395 VPVTIPHAT	27 LSVLATVHV	249 YFPNPVRTV			
30 LATVHVGQR	391 FSSFVPTI	24 LLLL SVLAT	248 QYFPNPVRT			
532 AVQNLQAKE	388 AMRFSSFVP	23 LLLL SVLA	247 LQYFPNPVVR			
501 AKMNF SYGL	385 LYEA MRFSS	12 PLNPLSIQ	243 VMPWLQYFP			
495 ANPNEPAKM	369 LPCMGDQPN	10 PWPLNPLSI	241 VDVMPWLQY			
488 AHQCDFRAN	357 QAELDQVVG	3 TSLSPNDPW	240 LVDVMPWLQ			
443 ARFLDKDGL	354 TRVQAELDQ	533 VQNLQAKET	210 FGCRYSHDD			
405 ANTSVLGYH	306 GDSHGGGAR	529 LDSAVQNLQ	208 VCFG CRYSH			
402 ATTANTS	280 CESLRPGAA	523 RESMELLD	205 MSAVCFGC			
388 AMRFSSFVP	277 LRHCESLRP	522 LRESMELLD	204 VMSAVCFG			
383 AFLYEAMRF	258 FREFEQLNR	506 SYGLTIKPK	203 NVMSAVCFG			
358 AELDQVVG	247 LQYFPNPVVR	505 FSYGLTIKP	200 AVANVMSAV			
338 ALQWL LLF	225 LSHNEEFGR	503 MNFSYGLTI	184 GSADGAFLD			
313 ARLDLENVP	214 YSHDDPEFR	500 PAKMNF SYG	175 RELVALLVR			
300 AEKKAAGDS	212 CRYSHDDPE	498 NEPAKMNF	174 ARELVALLV			
295 AFILSAEKK	211 GCRYSHDDP	491 CDFRANPNE	166 LEGHVLSEA			
288 APRDMMDAF	204 VMSAVCFG	483 FISILAHQC	155 FFTRQPRSR			
237 AGSLVDVMP	201 VANVMSAVC	476 SKMQLFLFI	137 YSEHWKVQR			
207 AVCFG CRY	178 VALLVRGSA	469 RCIGEELSK	135 GHYSEHWKV			
202 ANVMSAVCF	152 MRNFFTRQP	468 RRCIGEELS	129 GRSMAFGHY			
189 AFLDPRPLT	134 FGHYSEHWK	460 VMIFS VGR	125 VVSGGRSMA			
186 ADGAFLDPR	111 GSAFADRPA	451 LINKDLTSR	121 ASFRVVSGG			
179 ALLVRG SAD	110 QGSAFADRP	445 FLDKDGGLIN	119 AFASFRVVS			
174 ARELVALLV	78 ARR YGDVFQ	444 RFLDKDGGLI	111 GSAFADRPA			
148 AHSMMRNFF	75 ARLARRYGD	441 DPARFLKD	98 NGERAIHQ			
133 AFGHYSEHW	70 AHLSFARLA	433 KWPNPENFD	87 IRLGSCP IV			
121 ASFRVVSGG	44 RRQLRSAPP	429 HDPLKWPNP	85 FQIRLGSCP			
115 ADRPAFASF	41 RQRRRQLRS	426 SVNHDPLK	67 GQAAHLSFA			
106 ALVQQGSAF	40 LRQRRRQLR	425 WSVNHDPLK	35 VQRLLLRQR			
102 AIHQALVQQ	37 QRLLRQRRR	422 VNQWSVNHD	33 VHVGQRLLR			
78 ARR YGDVFQ	3 TSLSPNDPW	418 TVVFVNQWS	21 TLL LLLS			
75 ARLARRYGD	HLA-A26 Decamers		20 QTLL LLLS			
65 AVGQAAHLS	Pos 1234567890		3 TSLSPNDPW			
50 APPGPFAWP	333 DTLSTALQWL					
31 ATVHVGQRL						
HLA-A*0203 Decamers						
Pos 1234567890						
56 AWPLIGNAAA	527 ELLDSAVQNL	366 RDRLPCM				
296 FILSAEKKAA	474 ELSKMQLFLF	363 VVGRDRRLPC				
279 HCESLRPGA	326 DIFGASQDTL	353 QTRVQAELD				
139 EHWKVQRRAA	403 TTANTS	344 LLFTRYPDV				
61 GNAAAVGQAA	125 VVSGGRSMAF	343 LLLFTRYPD				
55 FAWPLIGNAA	83 DVFQIRLGSC	340 QWLLL FTR				
193 PRPLTVVAVA	380 YVLAFLYEA	326 DIFGASQDT				
112 SAFADRPAFA	363 VVGRDRRLPC	322 ATITDIFGA				
106 ALVQQGSAFA	336 STALQWL LLL	319 NVPATITDI				
297 ILSAEKKAA	255 RTVFRFEQL	312 GARLDLEN				
	181 LVRGSA	310 GGGGARLDLE				
	21 TTLL LLLS	304 AAGD SHGGG				

280 CESLRPGAAP	17 SIQQTTLLLL	301 EKKAAGDSH	
140 HWKVQRRAAH	520 VTLRESMELL	300 AEKKAAGDS	
62 NAAAVGQAAH	262 EQLNRNFSNF	294 DAFILSAEK	
57 WPLIGNAAAV	240 LVDVMPWLQY	292 MMADFILSA	
529 LDSAVQNLQA	88 RLGSCPIVVL	291 DMMDAFILS	
523 RESMELLDSEA	65 AVGQAAHLSF	287 AAPRDMMDA	
492 DFRANPNEPA	319 NVPATITDIF	274 DKFLRHCES	
486 ILAHQCDFRA	267 NFSNFIILDKF	273 LDKFLRHCE	
479 QLFLFISILA	519 NVTLRESMEL	270 NFILDKFLR	
434 WPNPENFDPA	431 PLKWPNPENF	266 RNFSNFIID	
396 PVTIPHATTA	517 KVNVTLRESM	262 EQLNRNFSN	
393 SFVPVTIPHA	455 DLTSRVMIFS	258 FREFEQLNR	
379 PYVLAFLYEA	377 NLPYVLAFLY	257 VFREFEQLN	
374 DQPNLPYVLA	176 ELVALLVRGS	255 RTVFREFEQ	
349 YPDVQTRVQA	142 KVQRRAAHSM	246 WLQYFPNPV	
329 GASQDTLSTA	76 RLARRYGDVF	241 VDVMPLQY	
321 PATITDIFGA	46 QLRSAPPGPF	233 RTVGAGSLV	
313 ARLDLENVPA	469 RCIGEELSKM	222 RELLSHNEE	
304 AAGDSHGGGA	408 SVLGYHIPKD	221 FRELLSHNE	
295 AFILSAEKKA	242 DVMPWLQYFP	218 DPEFRELLS	
291 DMMDAFILSA	196 LTVVAVANVM	211 GCRYSHDDP	
286 GAAPRDMMDA	31 ATVHVGQRLL	204 VMSAVCFG	
278 RHCESLRPGA	4 SLSPNDPWPL	203 NVMSAVCFG	
228 NEEFGRTVGA	510 TIKPKSFKVN	185 SADGAFLDP	
198 VVAVANVMSA	447 DKDGLINKDL	181 LVRGSADGA	
191 LDPRPLTVVA	417 DTVVFVNQWS	180 LLVRGSA	
180 LLVRGSA	413 HIPKDTVVVF	178 VALLVRGSA	
177 LVALLVRGSA	322 ATITDIFGAS	174 ARELVALLV	
170 VLSEARELVA	274 DKFLRHCESL	166 LEGHVLSEA	
165 VLEGHVLSEA	249 YFPNPVRTVF	162 SRQVLEGHV	
138 SEHWKVQRRA	198 VVAVANVMSA	161 RSRQVLEGH	
124 RVVSGGRSMA	164 QVLEGHVLSE	153 RNFFTRQPR	
110 QGSAFADRPA	114 FADRPAPASF	145 RRAAHSMMR	
104 HQALVQQGSA	102 AIHQALVQQG	128 GGRSMAFGH	
97 LNGERAIHQ	38 RLLRQRRRQL	127 SGGRSMAFG	
93 PIVVLNGERA	481 FLFISILAHQ	122 SFRVVSGGR	
69 AAHLSFARLA	421 FVNQWSVNHD	121 ASFRVVSGG	
66 VGQAAHLSFA	385 LYeamrfssf	105 QALVQQGSA	
60 IGNAAAVGQA	359 ELDQVVGDR	104 HQALVQQGS	
54 PFAWPLIGNA	334 TLSTALQWLL	97 LNGERAIHQ	
47 LRSAPPGPFA	287 AAPRDMMDAF	92 CPIVVLNG	
41 RQRRRQLRSA	271 FILDKFLRHC	91 SCPIVVLNG	
22 TLLLLLSQLA	165 VLEGHVLSEA	86 QIRLGSCPI	
530 DSAVQNLQAK	146 RAAHSMMRNF	80 RYGDVFQIR	
524 ESMELLDSEA	128 GGRSMAFGHY	76 RLARRYGDV	
493 FRANPNEPAK	34 HVGQRLLRQR	75 ARLARRYGD	
487 LAHQCDFRAN	15 PLSIQQTLL	65 AVGQAAHLS	
480 LFLFISILAH	12 PLNPLSIQQT	56 AWPLIGNAA	

435 PNPENFDPAR	473 EELSKMQLFL	52 PGFAWPLI
397 VTIPHATTAN	472 GEELSKMQLF	45 RQLRSAPPG
394 FVPVTIPHAT	459 RVMIFSVGKR	40 LRQRRRQLR
380 YVLAFLYeam	456 LTSRVMIFSV	25 LLLSVLATV
375 QPNLPYVLAF	454 KDLTSRVMIF	21 TTLLLLLSV
350 PDVQTRVQAE	450 GLINKDLTSR	14 NPLSIQQTT
330 ASQDTLSTAL	445 FLDKDGLINK	13 LNPLSIQQT
322 ATITDIFGAS	412 YHIPKDTVVF	11 WPLNPLSIQ
314 RLDLENVPAT	397 VTIPHATTAN	1 MGTSLSPND
305 AGDSHGGAR	376 PNLPYVLAFL	
292 MMDAFILESAE	375 QPNLPYVLAFL	
287 AAPRDMMDAF	346 FTRYPDVQTR	
229 EEFGRTEVGAG	340 QWLLLLFTRY	
199 VAVANVMSAV	337 TALQWLLLLF	
194 RPLTVVAVAN	314 RLDLENVPAT	
192 DPRPLTVVAV	259 REFEQLNRNF	
181 LVRGSADGAF	252 NPVRTVFRF	
178 VALLVGRGSA	241 VDVMPWLQYF	
171 LSEARELVAL	235 VGAGSLVDVM	
166 LEGHVLSEAR	234 TVGAGSLVDV	
125 VVSGGRSMAF	229 EEFGRTEVGAG	
113 AFADRPFAFAS	223 ELLSHNEEFG	
111 GSAFADRPFAF	220 EFRELLSHNE	
107 LVQQGSAFAD	215 SHDDPEFREL	
105 QALVQQGSAF	190 FLDPRPLTVV	
98 NGERAIHQAL	187 DGAFLDPRPL	
94 IVVNLGERAI	68 QAAHLSFARL	
70 AHLSFARLAR	20 QTLLLLLSV	
67 GQAAHLSFAR	7 PNDPWPLNPL	
48 RSAPPGPFAW	509 LTIKPKSFKV	
42 QRRRQLRSAP	496 NPNEPAKMNF	
23 LLLSVLAT	461 M1ESVGKRRC	
531 SAVQNLQAKE	426 SVNHDPLKWP	
525 SMELLDLSAVQ	406 NTSQLGYHIP	
494 RANPNEPAKM	393 SFVPVTIPHAT	
488 AHQCDFRANP	382 LAFLYEAAMRF	
481 FLFISILAHQ	316 DLENVPATIT	
436 NPENFDPARF	230 EFGRTVGAGS	
398 TIPHATTANT	195 PLTVVAVANV	
395 VPVTIPHATT	192 DPRPLTVVAV	
381 VLAFLYEAAMR	172 SEARELVAL	
376 PNLPYVLAFL	171 LSEARELVAL	
351 DVQTRVQAE	119 AFASFRVVSG	
331 SQDTLSTALQ	71 HLSFARLARR	
323 TITDIFGASQ	29 VLATVHVGQR	
315 LDLENVPATI	530 DSAVQNLQAK	
306 GDSHGGARL	499 EPAKMNFSYG	
298 LSAEKKAAGD	478 MQLFLFISIL	
293 MDAFILESAEK	470 CIGEELSKMQ	
288 APRDMMDAFI	451 LINKDLTSRV	
281 ESLRPGAAAPR	439 NFDPARFLDK	
230 EFGRTVGAGS	419 VVFVNQWSVN	
200 AVANVMSAVC	398 TIPHATTANT	
195 PLTVVAVANV	343 LLLFTRYPDV	

182 VRGSADGAFL	324 ITDIFGASQD
179 ALLVRGSA	323 TITDIFGASQ
172 SEARELVALL	270 NFILDKFLRH
167 EGHVLSEARE	260 EFEQLNRRNFS
141 WKVQRRAAHS	256 TVFREFEQLN
126 VSGGRSMAFG	238 GSLVDVMPWL
114 FADRPFAFASF	212 CRYSHDDPEF
108 VQQGSAFADR	124 RVVSGGRSMA
99 GERAIHQALV	111 GSAFADRPAF
95 VVLNGERAIH	72 LSFARLARRY
71 HLSFARLARR	58 PLIGNAAAVG
68 QAAHLSFARL	24 LLLLSQLATV
63 AAAVGQAAHL	23 LLLLSQLAT
58 PLIGNAAAVG	498 NEPAKMNFSY
49 SAPPGPFAWP	494 RANPNEPAKM
43 RRRQLRSAPP	492 DFRANPNEPA
24 LLLLSQLATV	484 ISILAHQCDF
HLA-A*0203 Octamers	471 IGEELSKMQL
Pos 12345678	
531 SAVQNLQA	464 SVGKRRCIGE
525 SMELLDSEA	436 NPENFDPARF
494 RANPNEPA	394 FVPVTIPHAT
488 AHQCDFRA	374 DQPQLPYVLA
481 FLFISILA	362 QVVGRDRRLPC
436 NPENFDPA	338 ALQWLWLLFT
398 TIPHATTA	318 ENVPATITDI
395 VPVTIPHA	296 FILSAEKKAA
381 VLAFLYEAA	291 DMMDAFILSA
376 PNLPYVLA	282 SLRPGAAPRD
351 DVQTRVQA	233 RTVGAGSLVD
331 SQDTLSTA	205 MSAVCFGCRY
323 TITDIFGA	203 NVMSAVCFG
315 LDLENVPA	200 AVANVMSAVC
306 GDSHGGGA	
298 LSAEKKAA	197 TVVAVANVMS
297 ILSAEKKA	177 LVALLVRGSA
293 MDAFILSA	156 FTRQPRSRQV
288 APRDMMDA	107 LVQQGSAFAD
281 ESLRPGAA	
280 CESLRPGAA	105 QALVQQGSAF
230 EFGRTVGA	59 LIGNAAAVGQ
200 AVANVMSA	54 PFAWPLIGNA
195 PLTVVAVA	28 SVLATVHVQGQ
193 PRPLTVVA	18 IQQTLLLL
182 VRGSADGA	532 AVQNLQAKET
179 ALLVRGSA	507 YGLTIKPKSF
172 SEARELVAA	483 FISILAHQC
167 EGHVLSEA	480 LFLFISILAH
141 WKVQRRAA	
	418 TVVFVNQWSV
	402 ATTANTSVLG
	384 FLYEAMRFSS
	381 VLAFLYEAMR
	371 CMGDQPNLPY
	355 RVQAELDQVV

140 HWKVQRRA	283 LRPGAAPRDM
126 VSGGRSMA	222 RELLSHNEEF
114 FADRPAFA	218 DPEFRELLSH
112 SAFADRPA	216 HDDPEFRELL
108 VQQGSAFA	207 AVCFGCRYSH
106 ALVQQGSA	201 VANVMSAVCF
99 GERAIHQQA	169 HVLSEARELV
95 VVLNGERA	157 TRQPRSRQVL
71 HLSFARLA	147 AAHSMMRNFF
68 QAAHLSFA	96 VLNGERAIHQ
63 AAAVGQAA	95 VVLNGERAIH
62 NAAAVGQA	94 IVVLNGERA
58 PLIGNAAA	93 PIVVLNGERA
57 WPLIGNAA	86 QIRLGSCPIV
56 AWPLIGNA	63 AAAVGQAAHL
49 SAPPGPFA	50 APPGPFAWPL
43 RRRQLRSA	16 LSIQQTTLLL
24 LLLLSVLA	528 LLDASAVQNLQ
	524 ESMELLLDSAV
	521 TLRESMELLD
	500 PAKMNFSYGL
	486 ILAHQCDFRA
	485 SILAHQCDFR
	482 LFISILAHQC
	479 QLFLFISILA
	452 INKDLTSRVM
	396 PVTIPHATTA
	383 AFLYEAMRFS
	373 GDQPNLPYVL
	369 LPCMGDQPNL
	368 RLPCMGDQPN
	353 QTRVQAELDQ
	344 LLFTRYPDVQ
	330 ASQDTLSTAL
	308 SHGGGARLDL
	306 GDSHGGGARL
	297 ILSAEKKAAG
	272 ILDKFLRHCE
	253 PVRTVFRERE
	208 VCFGCRYSHD
	182 VRGSADGAFL
	170 VLSEARELVA
	143 VQRRAAHSM
106 ALVQQGSAFA	106 ALVQQGSAFA
98 NGERAIHQAL	98 NGERAIHQAL
80 RYGDVFQIRL	80 RYGDVFQIRL
39 LLRQRRRQLR	39 LLRQRRRQLR
32 TVHVGQRLLR	32 TVHVGQRLLR
30 LATVHVGQRL	30 LATVHVGQRL
26 LLSVLATVHV	26 LLSVLATVHV
2 GTSLSNDPW	2 GTSLSNDPW
513 PKSFKVNVTL	513 PKSFKVNVTL
508 GLTIKPKSFK	508 GLTIKPKSFK
466 GKRRCIGEEL	466 GKRRCIGEEL
442 PARFLDKDGL	442 PARFLDKDGL

438 ENFDPARFLD	
430 DPLKWPNPEN	
423 NQWSVNHDP	
401 HATTANTSVL	
367 DRLPCMGDQP	
360 LDQVVGRDRL	
301 EKKAAGDSHG	
295 AFILSAEKKA	
294 DAFILSAEKK	
289 PRDMMDAFL	
284 RPGAAPRDMM	
276 FLRHCESLRP	
257 VFREFEQLNR	
246 WLQYFPNPV	
239 SLVDVMPWLQ	
231 FGRTVGAGSL	
224 LLSHNEEFGR	
217 DDPEFRELLS	
180 LLVRGSA	
179 ALLVRGSA	
168 GHVLSEAREL	
154 NFFTRQPRSR	
123 FRVVSGGRSM	
113 AFADRP	
25 LLLSVLATVH	
22 TLLLLL	
14 NPLSIQQTTL	
9 DPWPLNPLSI	
515 SFKVNVTLRE	
437 PENFDPARFL	
420 VFVNQWSVNH	
409 VLGYHIPKDT	
390 RFSSFVPTI	
389 MRFSSFVPT	
345 LFTRYPDVQT	
342 LLLL	
341 WLLL	
335 LSTALQWLLL	
307 DSHGGARLD	
286 GAAPRDMMDA	
268 FSNFILDKFL	
264 LNRNFSNFI	
263 QLNRNFSNFI	
248 QYFPNPVRTV	
219 PEFRELLSHN	
173 EARELVALLV	
167 EGHVLSEARE	
162 SRQVLEGHVL	
155 FFTRQPRSRQ	
139 EHWKVQRRAA	
116 DRPAFASFRV	
101 RAIHQALVQQ	
49 SAPPGPFAWP	
514 KSFKVNVTLR	
504 NFSYGLTIKP	
503 MNFSYGLTIK	

446	LDKDGLINKD
444	RFLDKDGLIN
441	DPARFLDKDG
415	PKDTVVVFVNQ
372	MGDQPNLPYV
350	PDVQTRVQAE
292	MMDAFLSAE
281	ESLRPGAAAPR
275	KFLRHCESLR
266	RNFSNFIILDK
189	AFLDPRPLTV
185	SADGAFLDPR
145	RRAAHSMMRN
131	SMAFGHYSEH
126	VSGGRSMAFG
122	SFRVVSGGRS
108	VQQGSAFADR
100	ERAIHQALVQ
97	LNGERAIIHQA
90	GSCPIVVLNG
84	VFQIRLGSCP
79	RRYGDVFQIR
73	SFARLARRYG
53	GPFAWPLIGN
33	VHVGQRLLRQ
512	KPKSFKVNV
505	FSYGLTIKPK
497	PNEPAKMNF
487	LAHQCDFRAN
465	VGKRRCIGEE
462	IFSVGKRCI
449	DGLINKDLTS
440	FDPARFLDKD
434	WPNPENFDPA
414	IPKDTVVVFVN
387	EAMRFSSFVP
361	DQVVGRDRLP
358	AELDQVVGRD
357	QAELDQVVGR
354	TRVQAELDQV
329	GASQDTLSTA
327	IFGASQDTLS
311	GGARLDLE
309	HGGGARLDLE
251	PNPVRTVFRE
244	MPWLQYFPNP
209	CFGCRYSHDD
199	VAVANVMSAV
193	PRPLTVVAVA
184	GSADGAFLDP
175	RELVALLVRG
159	QPRSRRQVLEG
137	YSEHWKVQRR
133	AFGHYSEHWK
120	FASFRVVSGG

91 SCPIVVVLNGE	
10 PWPLNPLSIQ	
523 RESMELLD SA	
522 LRESMELLD S	
516 FKVNVTLRES	
477 KMQLFLFISI	
476 SKMQLFLFIS	
475 LSKMQLFLFI	
457 TSRVMIFSVG	
435 PNPNENFDPAR	
428 NHDPLKWPNP	
416 KDTVVVFVNQW	
388 AMRFSSFVPV	
379 PYVLAFLYEA	
321 PATITDIFGA	
298 LSAEKKAAGD	
258 FREFEQLN RN	
243 VMPWLQYFPN	
237 AGSLVDVMPW	
225 LSHNEEFGRV	
160 PRSRQVLEGH	
150 SMMRNFFTRQ	
132 MAFGHYSEHW	
117 RPAFASFRVV	
89 LGSCPIVVLN	
81 YGDVFQIRLG	
78 ARRYGDVFQI	
66 VGQAAHLSFA	
60 IGNAAAVGQA	
41 RQRRRQLRSA	
511 IKPKSFKVNV	
501 AKMNFSYGLT	
404 TANTSVLGYH	
391 FSSFVPVTIP	
378 LPYVLAFLYE	
366 RDRLPCM GDQ	
356 VQAELDQVVG	
339 LQWLLLLFTR	
303 KAAGDSHGGG	
290 RDMMDAFILS	
278 RHCESLRPGA	
277 LRHCESLRPG	
265 NRNFNSNFI LD	
204 VMSAVCFGCR	
202 ANVMSAVCFG	
174 ARELVALV LVR	
153 RNFFTRQPRS	
149 HSMMRNFFTR	
136 HYSEHWKVQR	
75 ARLARRYGDV	
48 RSAPPGPFAW	
27 LSVLATVHVG	

19 QQTTLLLLLS	
531 SAVQNLQAKE	
493 FRANPNEPAK	
491 CDFRANPNEP	
490 QCDFRANPNE	
460 VMIFSVGKRR	
453 NKDLTSRVMI	
365 GRDRLPCMGD	
349 YPDVQTRVQA	
347 TRYPDVQTRV	
328 FGASQDTLST	
325 TDIFGASQDT	
315 LDLENVPATI	
305 AGDSHGGGAR	
300 AEKKAAGDSH	
293 MDAFILSAEK	
285 PGAAPRDMMD	
250 FPNPVRTVFR	
236 GAGSLVDVMP	
188 GAFLDPRPLT	
141 WKVQRRAAHS	
140 HWKVQRRAAH	
121 ASFRVVSGGR	
118 PAFASFRVVS	
115 ADRPAFASFR	
112 SAFADRPAFA	
92 CPIVVLNGER	
62 NAAAVGQAAH	
61 GNAAAVGQAA	
56 AWPLIGNAAA	
55 FAWPLIGNAA	
51 PPGPFAWPLI	
526 MELLDASAVQN	
518 VNVTLRESME	
506 SYGLTIKPKS	
495 ANPNEPAKMN	
488 AHQCDFRANP	
463 FSVGKRRCIG	
458 SRVMIFSVGK	
443 ARFLDKDGLI	
432 LKWPNPENFD	
405 ANTSVLGYHI	
400 PHATTANTS	
392 SSFVPTIPH	
386 YEAMRFSSFV	
370 PCMGDQPNLP	
364 VGRDRLPCM	
348 RYPDVQTRVQ	
331 SQDTLSTALQ	
313 ARLDLENVP	
304 AAGDSHGGGA	
302 KKAAGDSHGG	

288 APRDMMDAFI	
280 CESLRPGAAP	
279 HCESLRPGAA	
273 LDKFLRHCES	
269 SNFILDKFLR	
247 LQYFPNPVRT	
228 NEEFGRTVGA	
227 HNEEFGRTVG	
226 SHNEEFGRTV	
214 YSHDDPEFRE	
194 RPLTVVAVAN	
191 LDPRPLTVVA	
186 ADGAFLDPRP	
178 VALLVRGSAD	
161 RSRQVLEGHV	
158 RQPRSRSQVLE	
144 QRRAAHSMMR	
109 QQGSAFADRP	
104 HQALVQQGSA	
103 IHQALVQQGS	
87 IRLGSCPIVV	
85 FQIRLGSCPI	
70 AHLSFARLAR	
67 GQAAHLSFAR	
64 AAVGQAAHLS	
57 WPLIGNAAAV	
45 RQLRSAPPGP	
43 RRRQLRSAPP	
42 QRRRQLRSAP	
35 VGQRLLRQRR	
13 LNPLSIQQTT	
8 ND PWPLNPLS	
6 SPNDPWPLNP	
5 LSPNDPWPLN	
3 TSLSPNDPWP	
534 QNLQAKETCQ	
529 LDSAVQNLQA	
525 SMEELLDQAVQ	
489 HQCDFRANPN	
468 RRCIGEELSK	
433 KWPNPENFDP	
429 HDPLKWPNE	
427 VNHDPLKWPN	
425 WSVNHDPWKW	
424 QWSVNHDPWK	
395 VPVTIPHATT	
332 QDTLSTALQW	
320 VPATITDIFG	
310 GGGARLDLEN	
299 SAEKKAAGDS	
261 FEQLNRNFSN	
254 VRTVFREFEQ	
245 PWLQYFPNPV	
232 GRTVGAGSLV	
221 FRELLSHNEE	

166	LEGHVLSEAR
163	RQVLEGHVLS
152	MRNFFTRQPR
151	MMRNFFTRQP
138	SEHWKVQRRA
135	GHYSEHWKVQ
134	FGHYSEHWKV
130	RSMAFGHYSE
127	SGGRSMAFGH
99	GERAIHQALV
82	GDVFQIRLGS
77	LARRYGDVFQ
74	FARLARRYGD
52	PGPFAWPLIG
47	LRSAPPGPFA
44	RRQLRSAPPG
40	LRQRRRQLRS
37	QRLLRQRRRQ
36	GQRLLRQRRR
11	WPLNPLSIQQ
1	MGTSLSPNDP

**Prediction of HLA binding peptides from cytochrome P450 1B1
using the algorithm on the BIMAS website
(http://bimas.dcrt.nih.gov/molbio/hla_bind/)**

HLA-allele	peptide length	rank	starting position in the protein	sequence	score
A1	9mer	1	372	MGDQPNLPY	31.25
		2	137	YSEHWKVQR	27
	10mer	1	240	LVDVmPWLQY	125
		2	439	NFDPArFLDK	25
A_1101	9mer	1	459	RVMIFSVGK	12
		2	408	SVLGYHIPK	6
	10mer	1	459	RVMIfSVGKR	2.4
		2	508	GLTIkPKSFK	1.2
A_0201	9mer	1	246	WLQYFPNPV	1215.769
		2	239	SLVDVMPWL	1107.961
	10mer	1	24	LLLLsVLATV	1006.209
		2	343	LLLFrRYPDV	656.223
A_0205	9mer	1	479	QLFLFISIL	84
		2	239	SLVDVMPWL	42
	10mer	1	478	MQLFIFISIL	114.24
		2	24	LLLLsVLATV	20.4
A3	9mer	1	150	SMMRNFFTR	54
		2	408	SVLGYHIPK	27
	10mer	1	508	GLTIkPKSFK	90
		2	445	FLDKdGLINK	60
A_3101	9mer	1	150	SMMRNFFTR	36
		2	460	VMIFSVGKR	8
	10mer	1	459	RVMIfSVGKR	36
		2	339	LQWLILLFTR	36
A_3302	9mer	1	72	LSFARLARR	15
		2	225	LSHNEEFGR	15
	10mer	1	281	ESLRpGAAPR	45
		2	359	ELDQvVGRDR	27
A24	9mer	1	213	RYSHDDPEF	220
		2	275	KFLRHCESL	60
	10mer	1	80	RYGDvFQIRL	480
		2	385	LYEAmRFSSF	180
A68.1	9mer	1	408	SVLGYHIPK	240
		2	459	RVMIFSVGK	240
	10mer	1	459	RVMIfSVGKR	400
		2	34	HVGQrLLRQR	400
B7	9mer	1	173	EARELVALL	120
		2	39	LLRQRRRQL	60
	10mer	1	50	APPGpFAWPL	240
		2	288	APRDmMDAFT	240
B8	9mer	1	39	LLRQRRRQL	160

		2	173	EARELVALL	48
	10mer	1	156	FTRQpRSRQV	12
		2	512	KPKSTKVNV	8
B14	9mer	1	443	ARFLDKDGL	100
		2	361	DQVVGRDRL	45
	10mer	1	38	RLLRqRRRQL	250
		2	75	ARLArRYGDV	200
B_2702	9mer	1	79	RRYGDVFQI	900
		2	443	ARFLDKDGL	300
	10mer	1	212	CRYShDDPEF	1000
		2	443	ARFLdKDGLI	300
B_2705	9mer	1	443	ARFLDKDGL	10000
		2	79	RRYGDVFQI	9000
	10mer	1	79	RRYGdVFQIR	15000
		2	468	RRCigEELSK	6000
B40	9mer	1	229	EEFGRTVGA	80
		2	172	SEARELVAL	40
	10mer	1	473	EELSkMQLFL	40
		2	172	SEAReLVALL	40
B60	9mer	1	172	SEARELVAL	640
		2	472	GEELSKMQL	352
	10mer	1	473	EELSkMQLFL	640
		2	172	SEAReLVALL	352
B61	9mer	1	229	EEFGRTVGA	60
		2	280	CESLRPGAA	20
	10mer	1	46	QLRSaPPGPF	120
		2	377	NLPYvLAFLY	80
B62	9mer	1	338	ALQWLLLLF	96
		2	341	WLLLLFTRY	96
	10mer	1	46	QLRSaPPGPF	120
		2	377	NLPYvLAFLY	80
B_3501	9mer	1	288	APRDMMDAF	120
		2	284	RPGAAPRDM	80
	10mer	1	284	RPGAAaPRDMM	80
		2	288	APRDMMDAF	48
B_3701	9mer	1	217	DDPEFRELL	200
		2	454	KDLTSRVMI	200
	10mer	1	148	AHSMMRNFF	39
		2	428	NHDPLKWPN	11.7
B_3801	9mer	1	148	AHSMMRNFF	39
		2	428	NHDPLKWPN	11.7
	10mer	1	148	AHSMMRNFF	39
		2	428	NHDPLKWPN	11.7
B_3901	9mer	1	135	GHYSEHWKV	60
		2	412	YHIPKDTVV	30
	10mer	1	215	SHDDpEFREL	540
		2	168	GHVVLsEAREL	180
B_3902	9mer	1	19	QQTTLLLLL	24

		2	374	DQPNLPYVL	24
	10mer	1	447	DKDGIINKDL	24
		2	478	MQLFIFISIL	24
<u>B_4403</u>	9mer	1	473	EELSKMQLF	120
		2	386	YEAMRFSSF	80
	10mer	1	498	NEPAKMNF SY	180
		2	222	RELLsHNEEF	80
<u>B_5101</u>	9mer	1	414	IPKDTVVVF	314.6
		2	387	EAMRFSSFV	200
	10mer	1	9	DPWPINPLSI	1600
		2	288	APRDmMDAFI	440
<u>B_5102</u>	9mer	1	117	RPAFASFRV	400
		2	188	GAFLDPRPL	302.5
	10mer	1	9	DPWPINPLSI	2200
		2	57	WPLIgNAAAV	660
<u>B_5103</u>	9mer	1	401	HATTANTS V	121
		2	387	EAMRFSSFV	110
	10mer	1	410	LGYHiPKDTV	132
		2	199	VAVAnVMSAV	121
<u>B_5201</u>	9mer	1	356	VQAELDQVV	396
		2	374	DQPNLPYVL	88
	10mer	1	478	MQLFIFISIL	90
		2	117	RPAFASFRVV	50
<u>B_5801</u>	9mer	1	238	GSLVDVMPW	105.6
		2	49	SAPPGPFAW	80
	10mer	1	48	RSAPPGPFAW	480
		2	146	RAAHsMMRNF	99

CLAIMS

1. A method of treating a patient that comprises or is at risk of comprising a cell that expresses cytochrome P450 1B1, said method comprising administering to said patient a cytotoxic T lymphocyte that kills said cell in a cytochrome P450 1B1-specific, major histocompatibility complex-restricted fashion.
5
2. The method of claim 1, wherein said cytotoxic T lymphocyte is autologous to said patient.
10
3. The method of claim 1, wherein said cytotoxic T lymphocyte is allogeneic to said patient.
15
4. The method of claim 1, wherein said cytotoxic T lymphocyte is generated by activation with an antigen presenting cell that has been pulsed with cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 that binds to a major histocompatibility complex molecule.
15
5. The method of claim 1, further comprising administering to said patient a cytotoxic T lymphocyte that kills a cell in said patient that expresses a second tumor associated antigen.
20
6. The method of claim 5, wherein said second tumor associated antigen is telomerase.
25
7. A method of treating a patient that comprises or is at risk of comprising a cell that expresses cytochrome P450 1B1, said method comprising administering to said patient an antigen presenting cell that activates in said patient a cytotoxic T lymphocyte that kills said cell in a cytochrome P450 1B1-specific, major histocompatibility complex-restricted fashion.
30

8. The method of claim 7, wherein said antigen presenting cell has been pulsed with cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 that binds to a major histocompatibility complex molecule,

5 9. The method of claim 7, further comprising administering to said patient an antigen presenting cell that activates in said patient a cytotoxic T lymphocyte that kills a cell in said patient that expresses a second tumor associated antigen.

10 10. The method of claim 9, wherein said second tumor associated antigen is telomerase.

11. A method of treating a patient that comprises or is at risk of comprising a cell that expresses cytochrome P450 1B1, said method comprising administering to said patient a peptide of cytochrome P450 1B1 that binds to a major histocompatibility complex molecule, wherein said peptide of cytochrome P450 1B1 is processed by an antigen presenting cell in said patient, which activates a cytotoxic T lymphocyte in said patient to kill said cell that expresses cytochrome P450 1B1 in a cytochrome P450 1B1-specific, major histocompatibility complex-restricted fashion.

20 12. The method of claim 11, wherein said peptide of cytochrome P450 1B1 is administered to said patient in association with an adjuvant.

13. The method of claim 11, further comprising administering to said patient a second tumor associated antigen or a peptide thereof that binds to a major histocompatibility complex molecule, wherein said second tumor associated antigen or said peptide thereof is processed by an antigen presenting cell in said patient, which activates a cytotoxic T lymphocyte in said patient to kill cells that express the second tumor associated antigen in a tumor associated antigen-specific, major histocompatibility complex-restricted fashion.

14. The method of claim 13, wherein said second tumor associated antigen is telomerase.

15. A method of treating a patient that comprises or is at risk of comprising a cell that expresses cytochrome P450 1B1, said method comprising administering to said patient a nucleic acid molecule encoding cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 that binds to a major histocompatibility complex molecule, wherein said nucleic acid molecule is expressed in said patient so that the polypeptide or peptide it encodes can be processed by an antigen presenting cell in said patient, which activates a cytotoxic T lymphocyte in said patient to kill said cell that expresses cytochrome P450 1B1 in a cytochrome P450 1B1-specific, major histocompatibility complex-restricted fashion.

16. The method of claim 15, wherein said nucleic acid molecule encoding cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 is in an expression vector.

17. The method of claim 15, further comprising administering to said patient a nucleic acid molecule encoding a second tumor associated antigen or a peptide thereof that binds to a major histocompatibility complex molecule, wherein said nucleic acid molecule is expressed in said patient so that the polypeptide or peptide that it encodes can be processed by an antigen presenting cell in said patient, which activates a cytotoxic T lymphocyte in said patient to kill cells that express the second tumor associated antigen in a tumor associated antigen-specific, major histocompatibility complex-restricted fashion.

18. The method of claim 17, wherein the second tumor associated antigen is telomerase.

19. The method of claim 1, 7, 11, or 15, wherein said patient comprises a tumor comprising cells that express cytochrome P450 1B1.

20. The method of claim 4 or 7, wherein said antigen presenting cell is a dendritic cell or a CD40-activated B cell.

5 21. The method of claim 4, 8, 11, or 15, wherein said peptide of cytochrome P450 1B1 binds to a class I major histocompatibility complex molecule.

10 22. The method of claim 21, wherein said class I major histocompatibility complex molecule is an HLA-A2 or an HLA-A3 molecule.

15 23. The method of claim 22, wherein said peptide of cytochrome P450 1B1 comprises the amino acid sequence of CYP239 (SEQ ID NO:1), CYP246 (SEQ ID NO:2), CYP190 (SEQ ID NO:3), or CYP528 (SEQ ID NO:4).

24. A method of assessing the level of immunity of a patient to cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 that binds to a major histocompatibility complex molecule, said method comprising measuring the level of cytotoxic T lymphocytes specific for cytochrome P450 1B1 or said peptide of cytochrome P450 1B1 in a sample from said patient.

25 25. The method of claim 24, wherein said sample is obtained from said patient before or after a cancer treatment is administered to said patient.

26. A cytochrome P450 1B1 peptide that binds to a major histocompatibility complex molecule.

27. The peptide of claim 26, consisting essentially of the amino acid sequence of CYP239 (SEQ ID NO:1), CYP246 (SEQ ID NO:2), CYP190 (SEQ ID NO:3), or CYP528 (SEQ ID NO:4).

28. An *ex vivo* generated cytotoxic T lymphocyte that specifically kills a cell expressing cytochrome P450 1B1 in a specific, major histocompatibility complex-restricted fashion.

5 29. An *ex vivo* generated antigen presenting cell that presents a peptide of a cytochrome P450 1B1 in the context of a major histocompatibility complex molecule.

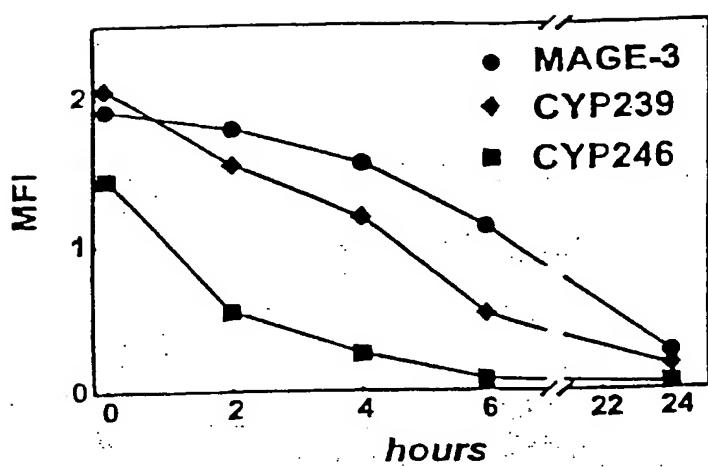
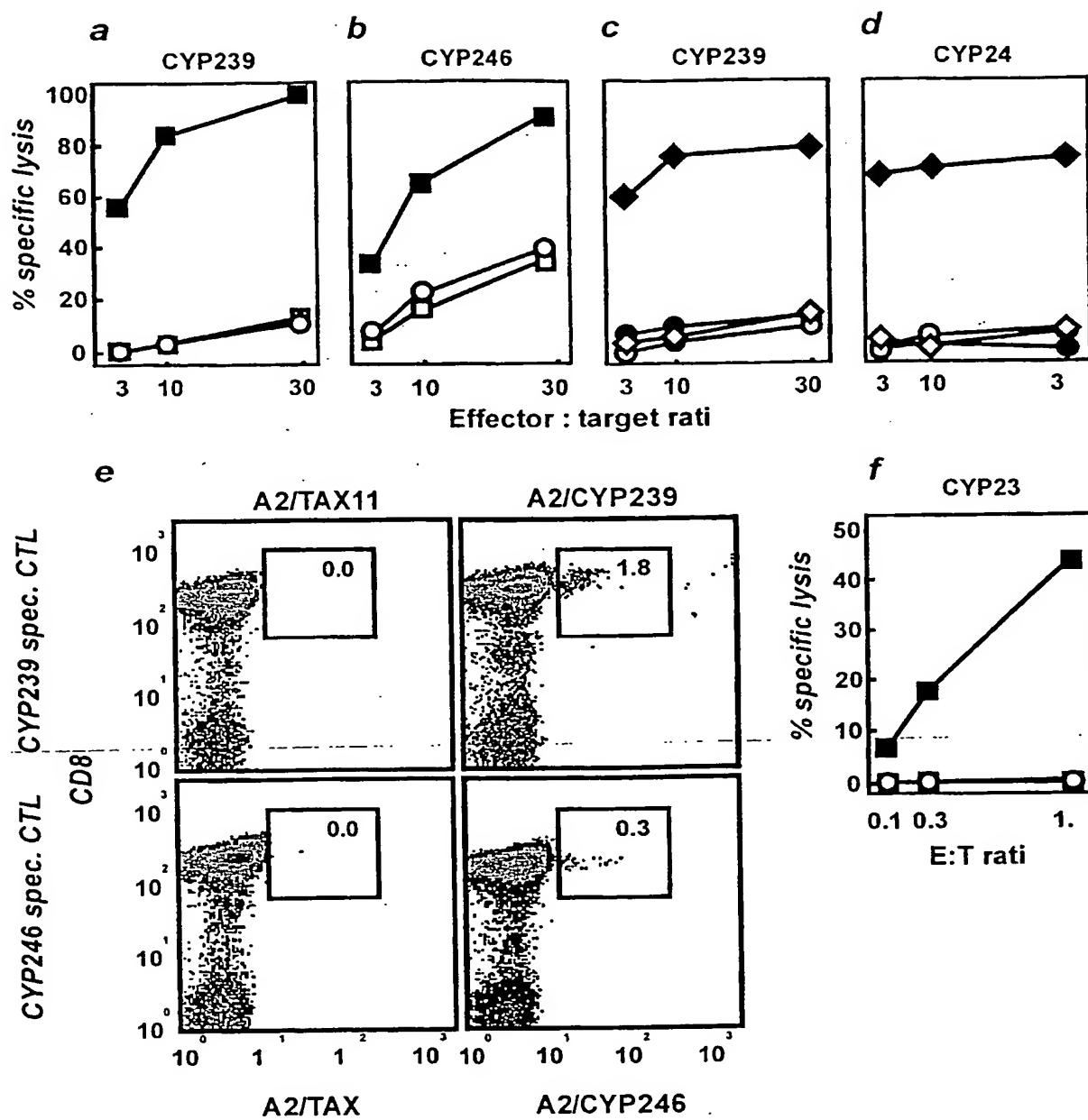


Fig. 1

FIGURE 2



**CYP239 SPECIFIC LYSIS OF PULSED CD40-B CELLS IS
DEPENDENT ON PEPTIDE CONCENTRATION**

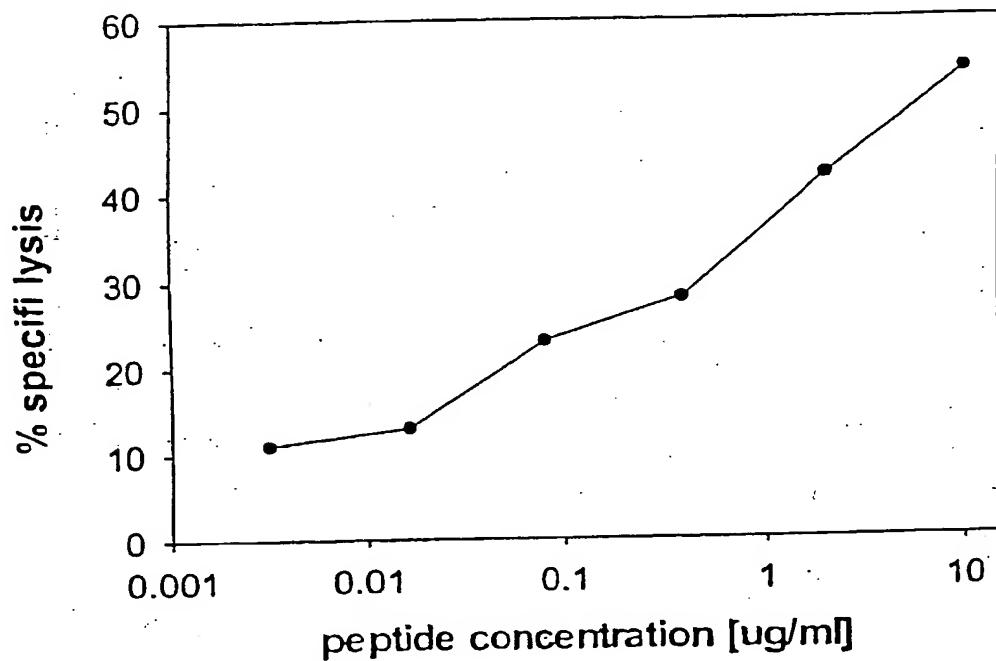
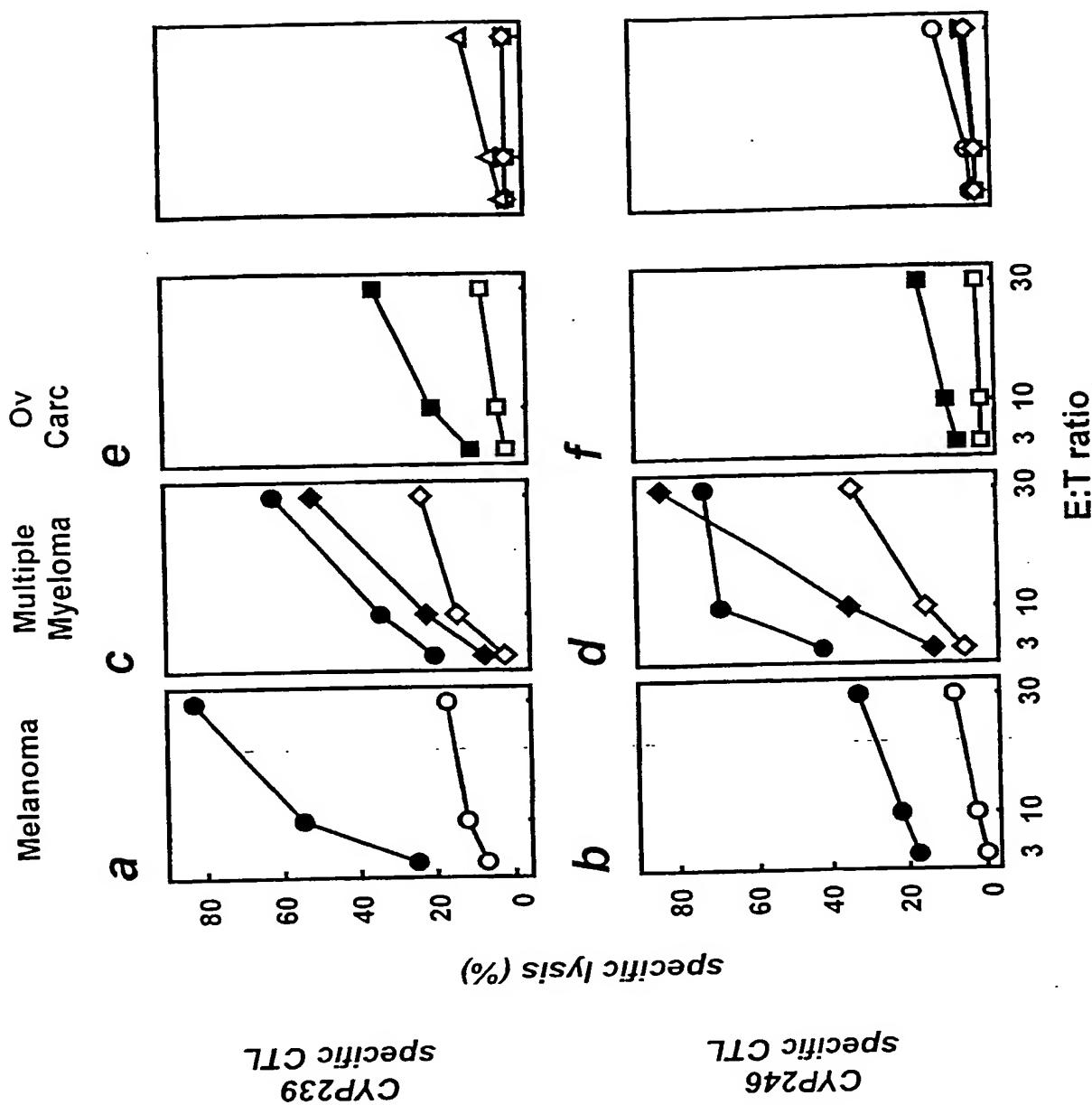


Fig. 3

FIGURE 4



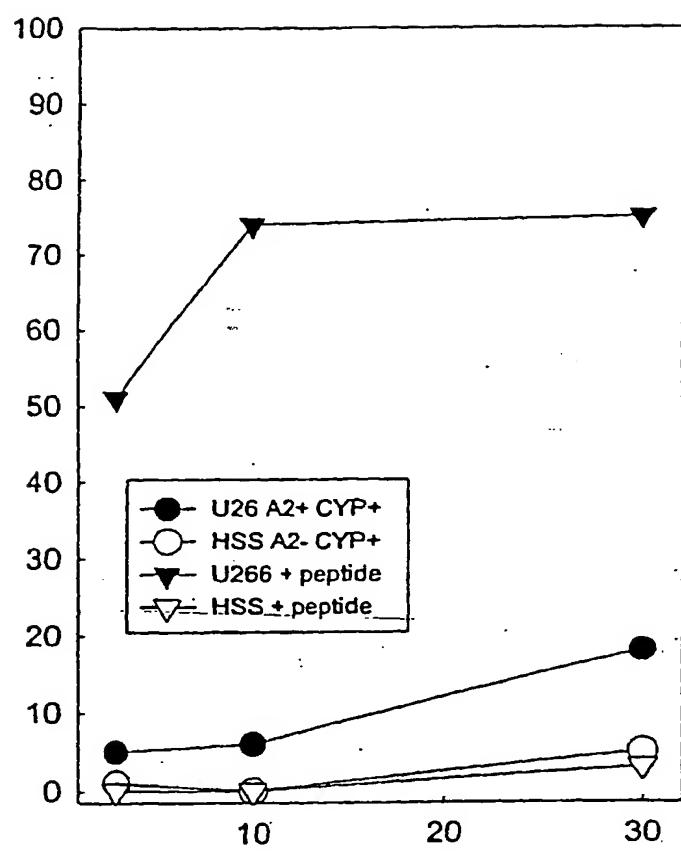
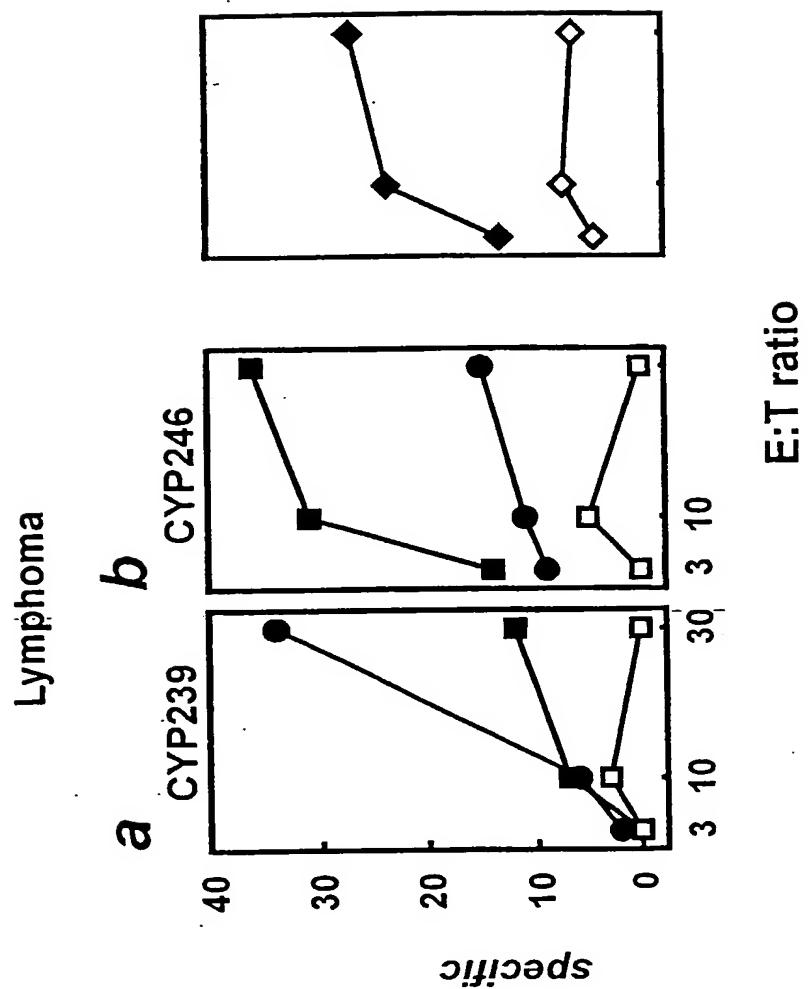


Fig. 5

FIGURE 6

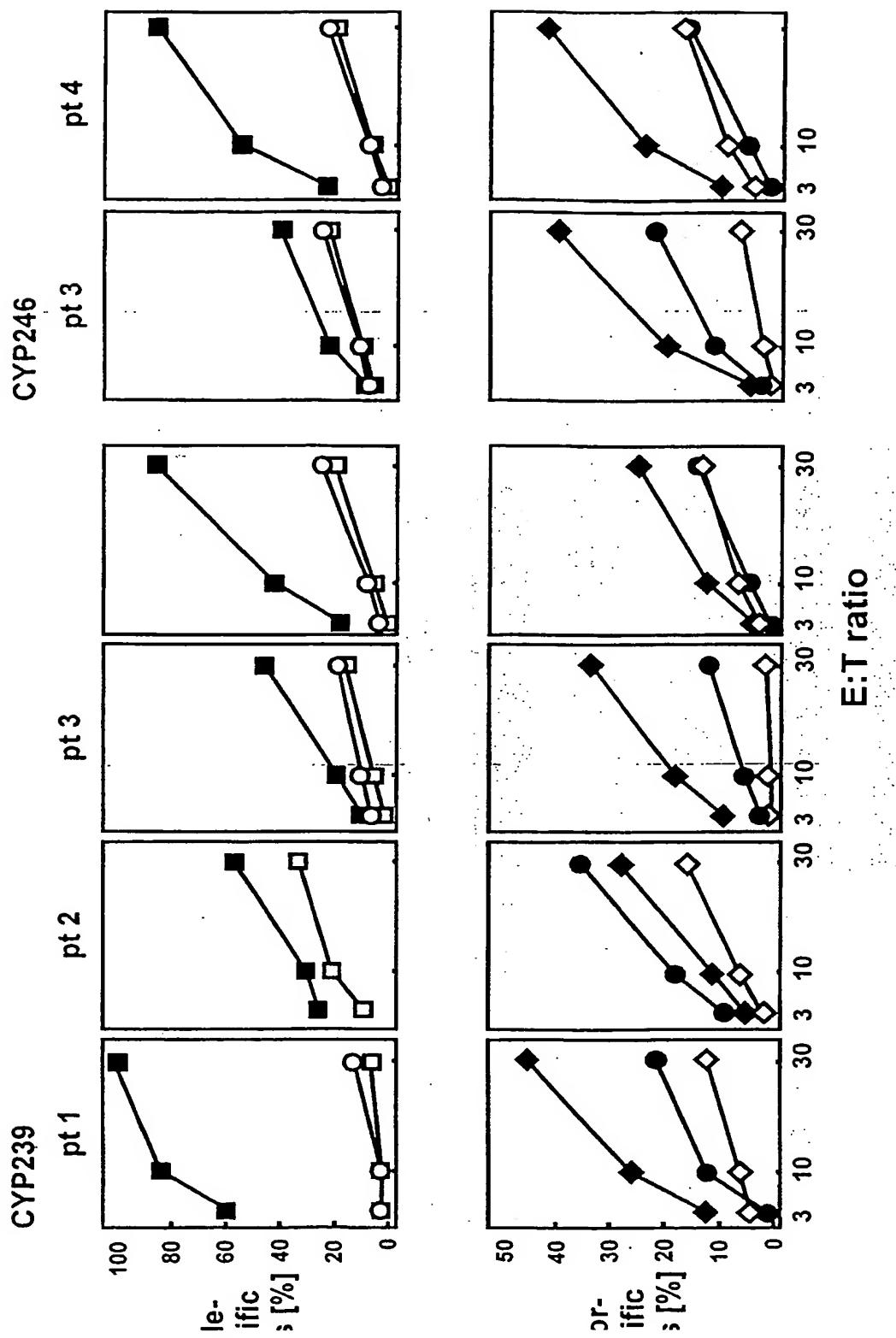
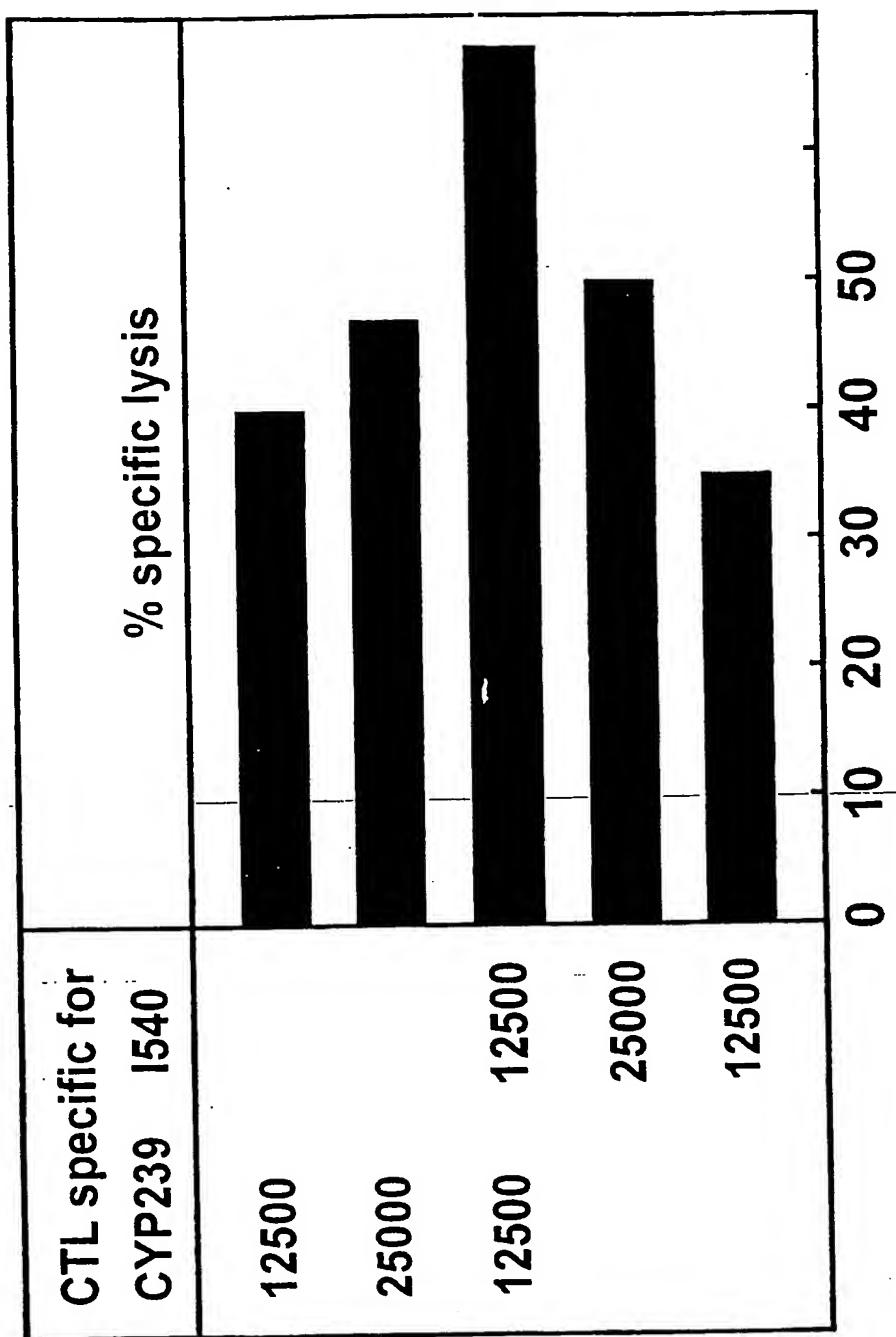


FIGURE 8

Use of heteroclitic peptides

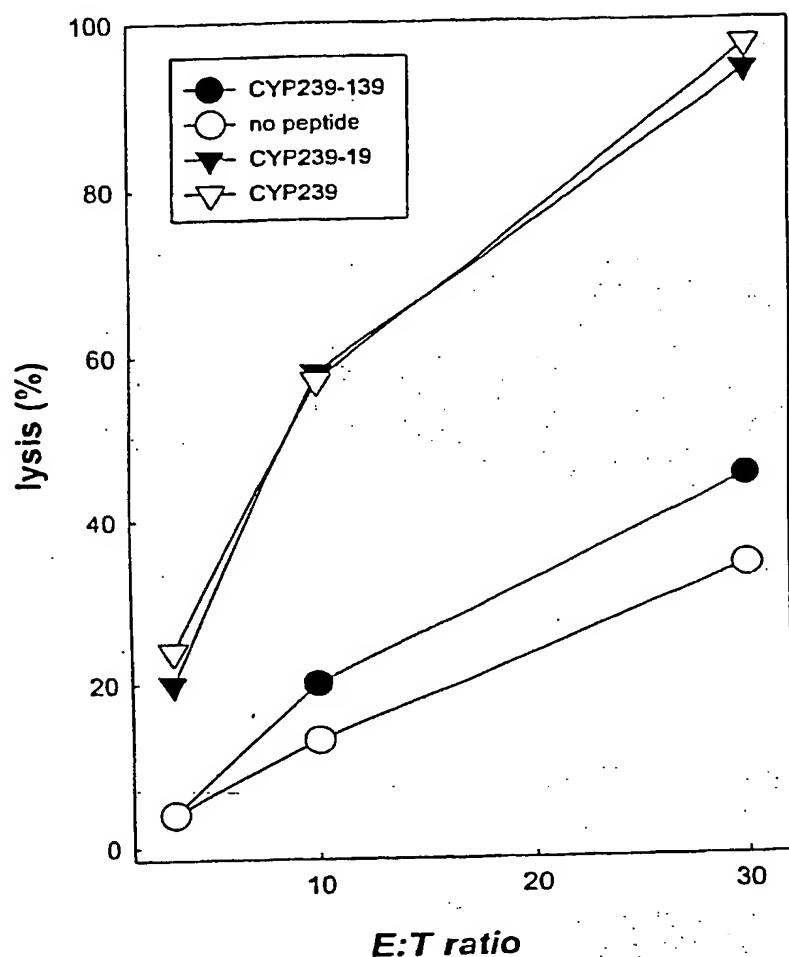


Fig. 9

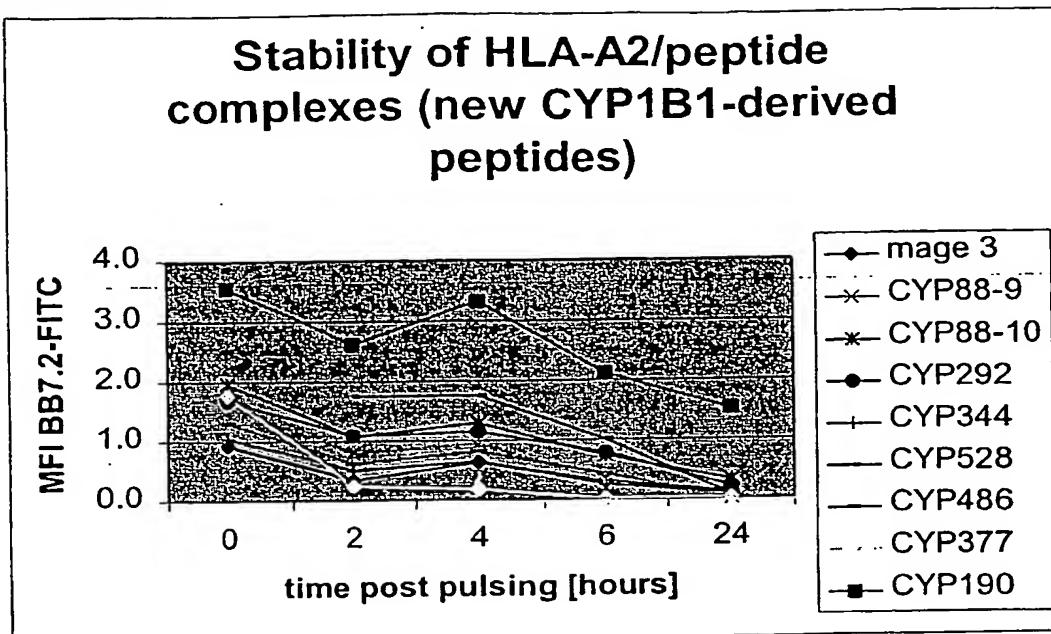
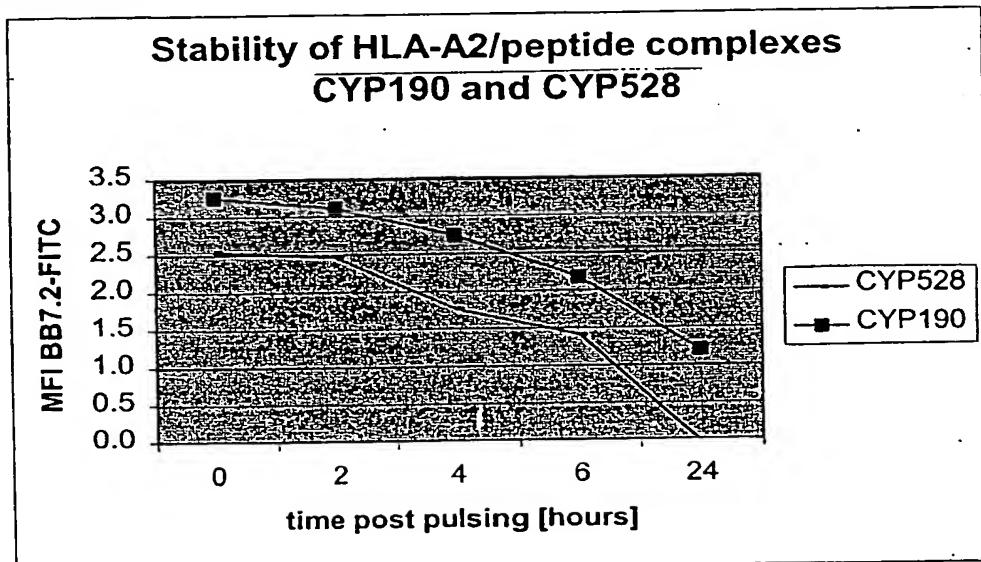
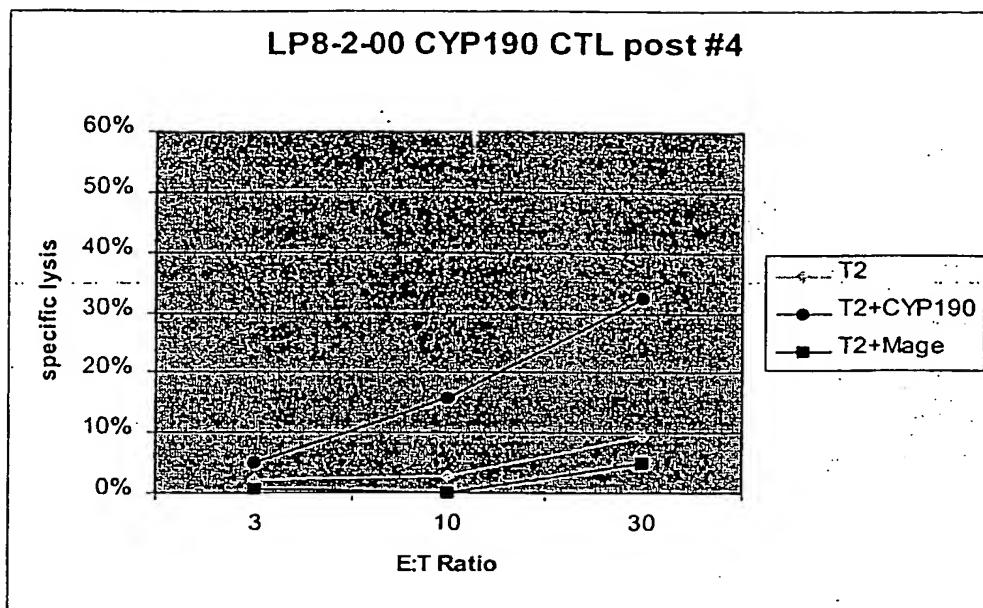
FIGURE 10**FIGURE 11**

FIGURE 12A



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FIGURE 12B

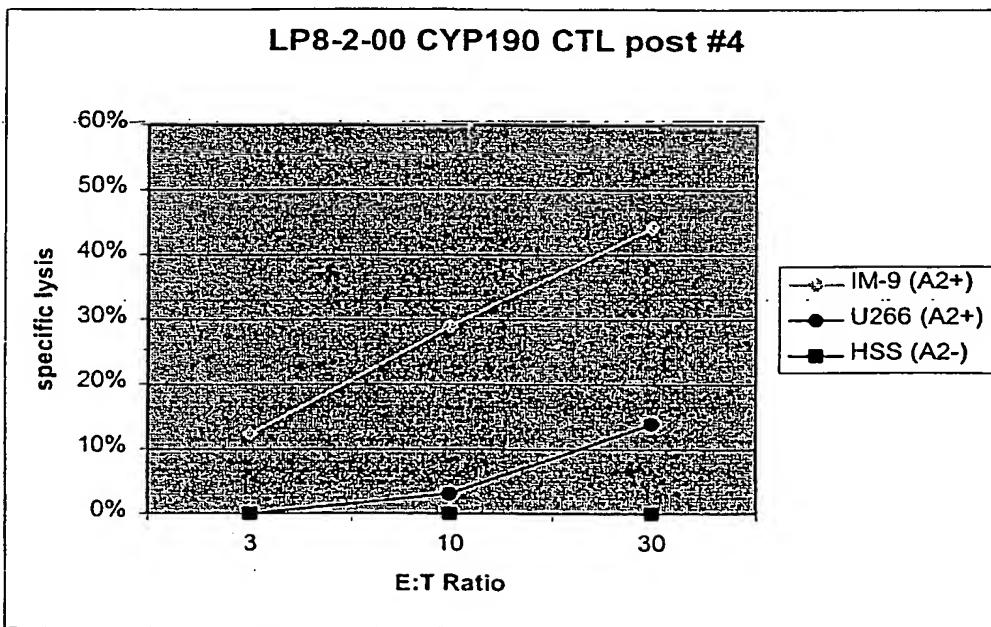


FIGURE 12C

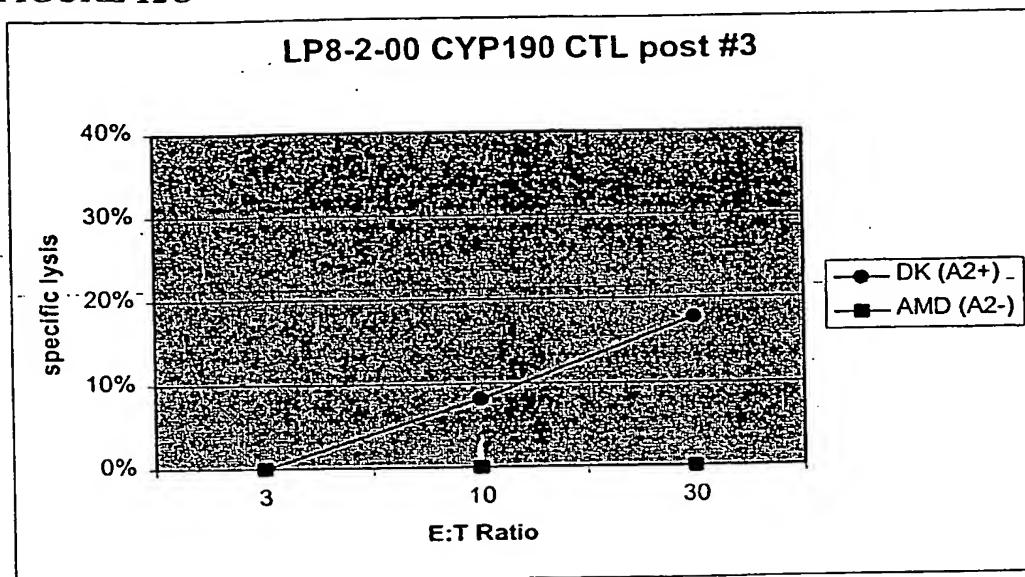
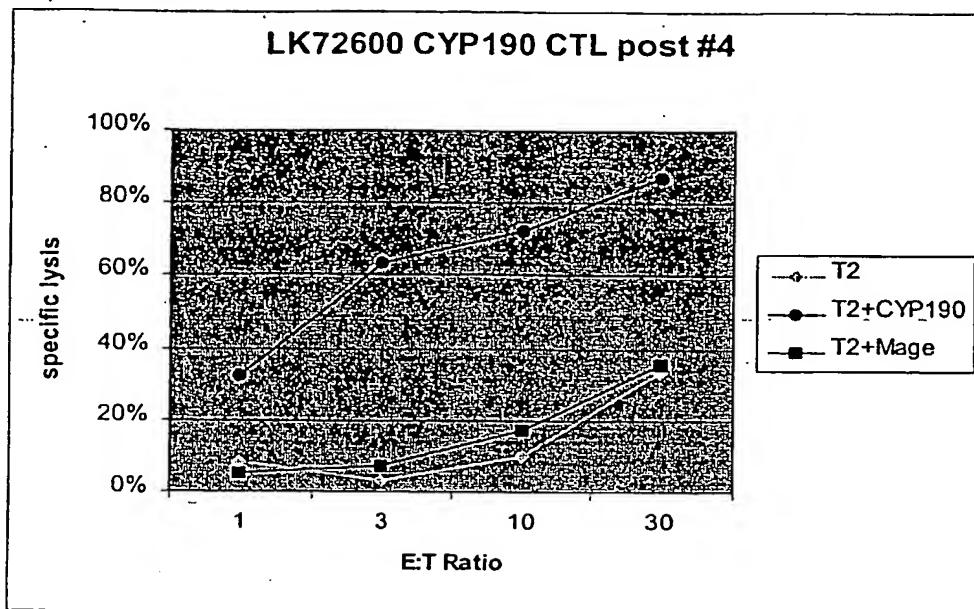


FIGURE 13A



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FIGURE 13B

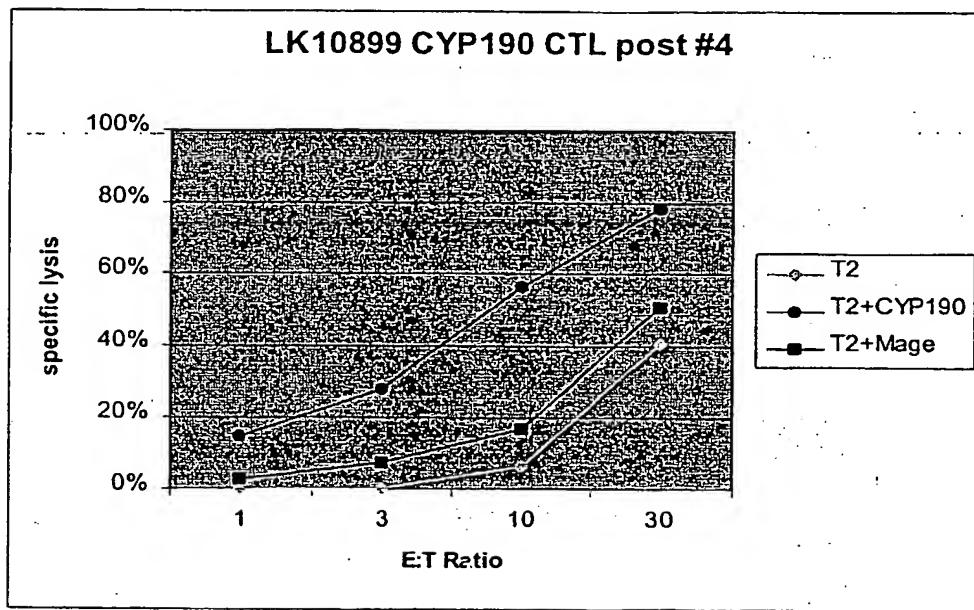


FIGURE 14 Generation and verification of CYP1B1specific tetramers

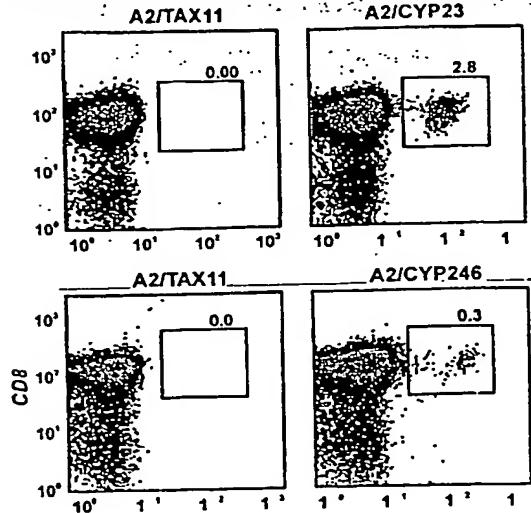


FIGURE 15 Analysis of MM pB samples

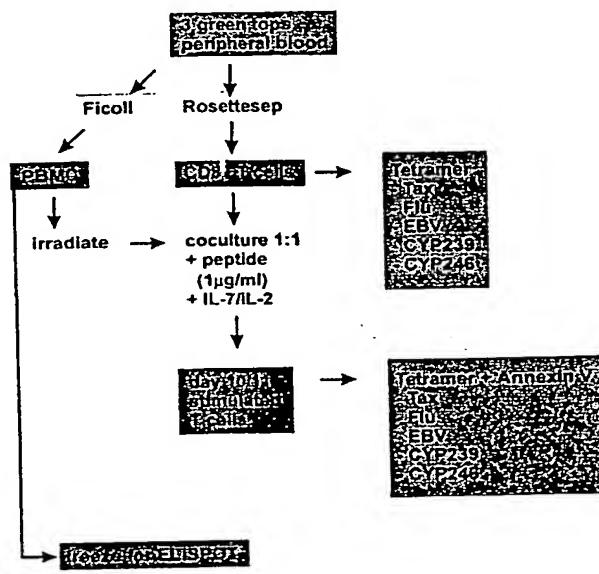
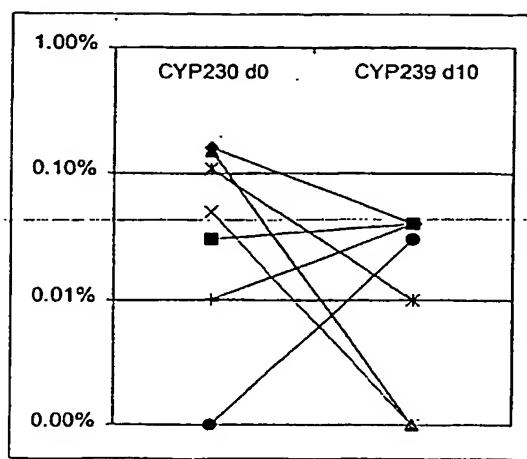
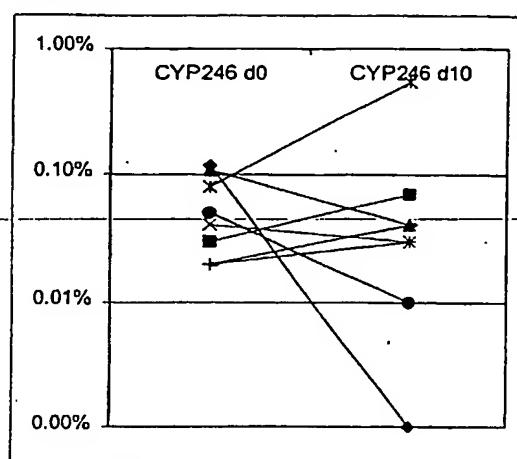


FIGURE 16

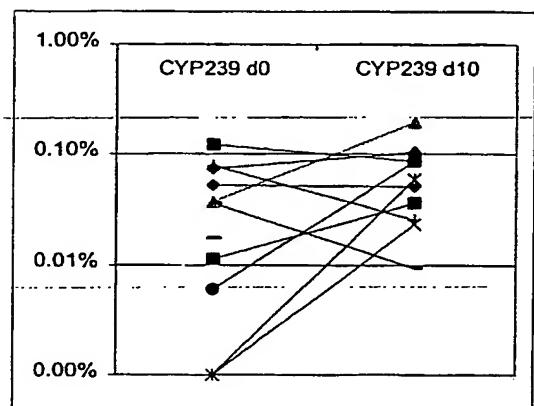
CYP239



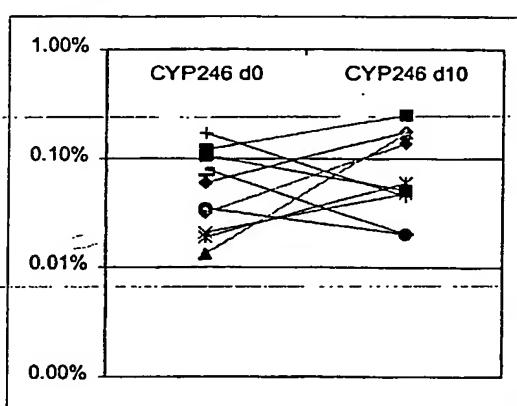
CYP246

**FIGURE 17**

CYP239



CYP246



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(71) Applicants (for all designated States except US):
DANA-FARBER CANCER INSTITUTE, INC. [US/US]; 44 Binney Street, Boston, MA 02115 (US).
TRUSTEES OF BOSTON UNIVERSITY [US/US]; 147 Bay State Road, Boston, MA 02215 (US).

(72) Inventors; and
(75) Inventors/Applicants (for US only): **SCHULTZE**,

Joachim, L. [DE/US]; 37 Auburn Street, Brookline, MA 02146 (US). VONDERHEIDE, Robert, H. [DE/US]; Apartment 801, 1284 Beacon Street, Brookline, MA 02115 (US). SHERR, David [US/US]; 39 Hastings Street, West Roxbury, MA 02132 (US). NADLER, Lee, M. [US/US]; 36 Cross Hill Road, Newton, MA 02159 (US). MAECKER, Britta [DE/US]; 368 Longwood Avenue, #21, Boston, MA 02215 (US). VON BERGWELT-BAILDON, Michael [DE/US]; 24 A Prentiss Street, Cambridge, MA 02140 (US).

(74) Agent: **CLARK, Paul, T.**; Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110-2214 (US).

(81) Designated States (national): CA, JP, US.

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(57) Abstract: The invention provides methods for conducting cancer immunotherapy and diagnosis using cytochrome P450 1B1 and peptide fragments thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/31513

A. CLASSIFICATION OF SUBJECT MATTER

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US CL : 424/93.21, 93.7, 184.1; 435/252.3, 325

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.21, 93.7, 184.1; 435/252.3, 325

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	Database DERWENT, Accession No. 2000-365402, HAHN et al. Universal tumor-associated antigens such as telomerase catalytic subunit capable of binding major histocompatibility complex molecule useful for diagnosis, prevention and treatment of cancer. Abstract, WO 00/25813 A1 (DANA FARBER CANCER INSTITUTE, INC) 11 May 2000, see abstract	1-6, 19-23 and 28
A, P	Database CAPLUS on ACS, Accession No. 2000:494217, HEIDEL et al. Cytochrome P4501B1 mediates induction of bone marrow cytotoxicity and preleukemia cells in mice treated with 7,12-dimethylbenz[a]anthracene. Cancer Res. 2000. Vol. 60. No. 13, pages 3454-3460, see abstract.	1-6, 19-23 and 28

 Further documents are listed in the continuation of Box C. See patent family annex.

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	document published prior to the international filing date but later than the priority date claimed		

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Authorized officer

TERRY J. DEY
SUSAN UNGAR PARALEGAL SPECIALIST

Telephone No. (703) 272-1300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/31513

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database CAPLUS on ACS, Accession No. 1999:203774, SPENCER et al. Quantitative analysis of constitutive and 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin-induced cytochrome P450 1B1 expression in human lymphocytes. <i>Cancer Epidemiology, Biomarkers Prev.</i> , 1999, Vol 8, No. 2 pages 139-146, see abstract	1-6, 19-23 and 28

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-6, 19-23 and 28

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

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B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

PIR_66, BIOSIS, BIOTECHNO, CAPLUS, EMBASE, ESBIOBASE, GENBANK, LIFESCI, MEDLINE, SCISEARCH, TOXLINE, TOXLIT

search terms: 450 CYP1b1, gene, treat, antigen presenting cell, cytotoxic, T-lymphocyte

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-6, and 19-23 and 28, drawn to a method of treating a patient with cytotoxic T cells.

Group II, claim(s) 7-10 and 19-23, drawn to a method of treating patients with an antigen presenting cell that activates cytotoxic T lymphocytes.

Group III, claim(s) 11-14 and 19-23, drawn to a method of treating a patient comprising administering a peptide of CYT p450 1B1.

Group IV, claim(s) 15-18 and 19-23, drawn to a method of treating a patient comprising administering a nucleic acid encoding CYT P450 1B1 or a peptide thereof.

Group V, claim(s) 24-25, drawn to a method of assessing the level of immunity in a patient.

Group VI, claim(s) 26-27, drawn to a peptide.

Group VI, claim(s) 29, drawn to an ex vivo generated antigen presenting cell.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

The claims are deemed to correspond to the species listed above in the following manner:

The following claims are generic:

Group I, claim 1, the species are

Species (a) SEQ ID NO:1

Species (b) SEQ ID NO:2

Species (c) SEQ ID NO:3

Species (d) SEQ ID NO:4, all of claim 23

Group II, claim 1, the species are

Species (a) SEQ ID NO:1

Species (b) SEQ ID NO:2

Species (c) SEQ ID NO:3

Species (d) SEQ ID NO:4, all of claim 23

Group III, claim 1, the species are

Species (a) SEQ ID NO:1

Species (b) SEQ ID NO:2

Species (c) SEQ ID NO:3

Species (d) SEQ ID NO:4, all of claim 23

Group IV, claim 1, the species are

Species (a) SEQ ID NO:1

Species (b) SEQ ID NO:2

Species (c) SEQ ID NO:3

Species (d) SEQ ID NO:4, all of claim 23

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Group VI, claim 1, the species are
Species (a) SEQ ID NO:1
Species (b) SEQ ID NO:2
Species (c) SEQ ID NO:3
Species (d) SEQ ID NO:4, all of claim 27

The inventions listed as Groups I-VI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The first invention claimed, claims 1-6, 20-23 and 28 is considered the main invention. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories thereto will be considered as the main invention of the claims, see PCT Article 17(3)(a) and 1.476(c). After that, all other products and methods will be broken out as separate groups. (See 37 CFR 1.475(d). All of the other groups are drawn to products or methods not recited in the main invention.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

The species recited relate to products with different sequences and therefore different structures and functions.